A PROSPECTIVE OBSERVATIONAL STUDY TO COMPARE THE PULSE OXIMETRIC SATURATION (Spo2) /FRACTION OF INSPIRED OXYGEN (Fio2) (SF RATIO) AND PARTIAL PRESSURE OF OXYGEN (Pao2) / Fio2 (PF RATIO) AMONG CRITICALLY ILL CHILDREN REQUIRING RESPIRATORY SUPPORT IN A PAEDIATRIC INTENSIVE CARE UNIT

A dissertation submitted to Tamil Nadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of requirement for the M.D Pediatrics degree examination to be held in April, 2017.

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Dissertation submitted to

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IN

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By

SHAJIN. T.

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DEPARTMENT OF PAEDIATRICS

CHRISTIAN MEDICAL COLLEGE

VELLORE

APRIL 2017

CERTIFICATE

This is to certify that this dissertation,

"**A PROSPECTIVE OBSERVATIONAL STUDY TO COMPARE THE PULSE OXIMETRIC SATURATION (Spo2) /FRACTION OF INSPIRED OXYGEN (Fio2) (SF RATIO) AND PARTIAL PRESSURE OF OXYGEN (Pao2) / Fio2 (PF RATIO) AMONG CRITICALLY ILL CHILDREN REQUIRING RESPIRATORY SUPPORT IN A PAEDIATRIC INTENSIVE CARE UNIT"** is the bonafide work of Dr.Shajin.T. under my supervision in the Department of Paediatric Intensive Care Unit, Christian Medical College Vellore in partial fulfillment of the requirements for the award of M.D, Pediatrics Examination of Tamil Nadu Dr. M.G.R Medial University to be held in April 2017 and no part thereof has been submitted for any other degree.

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CERTIFICATE BY THE HEAD OF THE DEPARTMENT/ PRINCIPAL

This to certify that this dissertation,

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DECLARATION

I, Shajin.T., do hereby declare that the dissertation titled "**A PROSPECTIVE OBSERVATIONAL STUDY TO COMPARE THE PULSE OXIMETRIC SATURATION (Spo2) /FRACTION OF INSPIRED OXYGEN (Fio2) (SF RATIO) AND PARTIAL PRESSURE OF OXYGEN (Pao2) / Fio2 (PF RATIO) AMONG CRITICALLY ILL CHILDREN REQUIRING RESPIRATORY SUPPORT IN A PAEDIATRIC INTENSIVE CARE UNIT"** is a genuine record of research done by me under the supervision and guidance of Dr. Ebor Jacob James, Professor in the Department of Paediatric Intensive Care Unit, Christian Medical College, Vellore and has not previously formed the basis of award of any degree, diploma, fellowship or other similar title of any university or institution.

Vellore Dr. Shajin.T

Date

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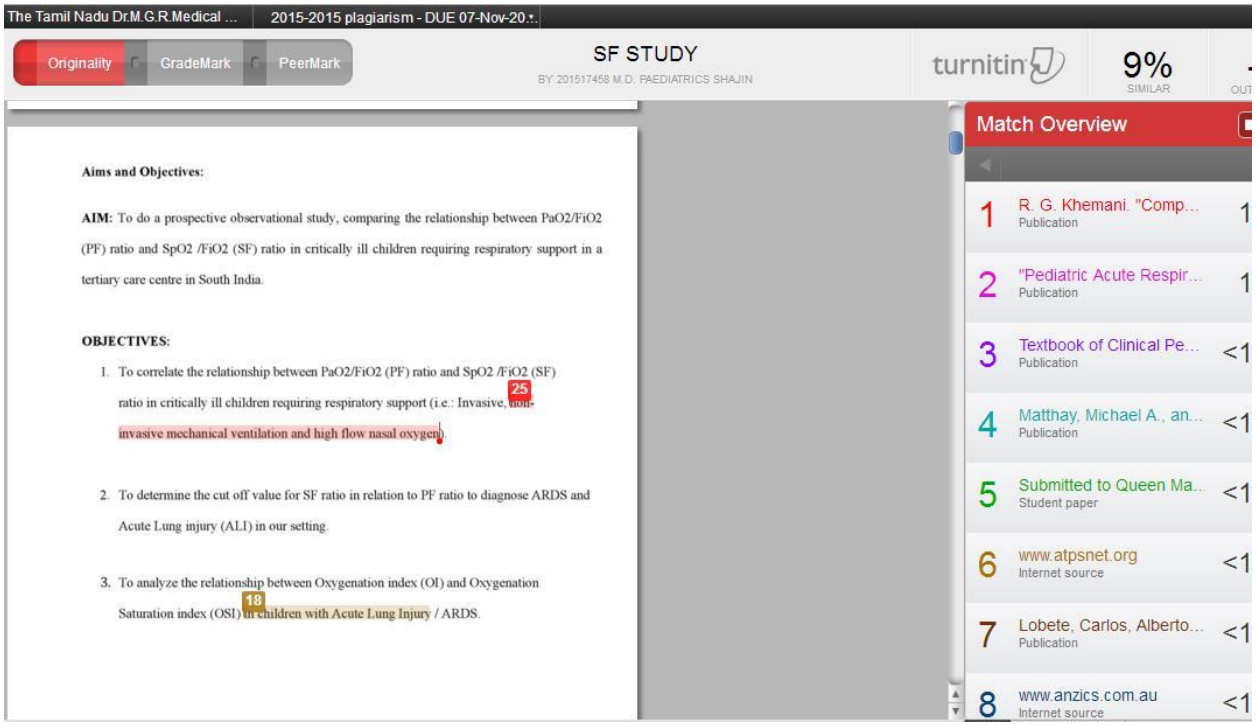
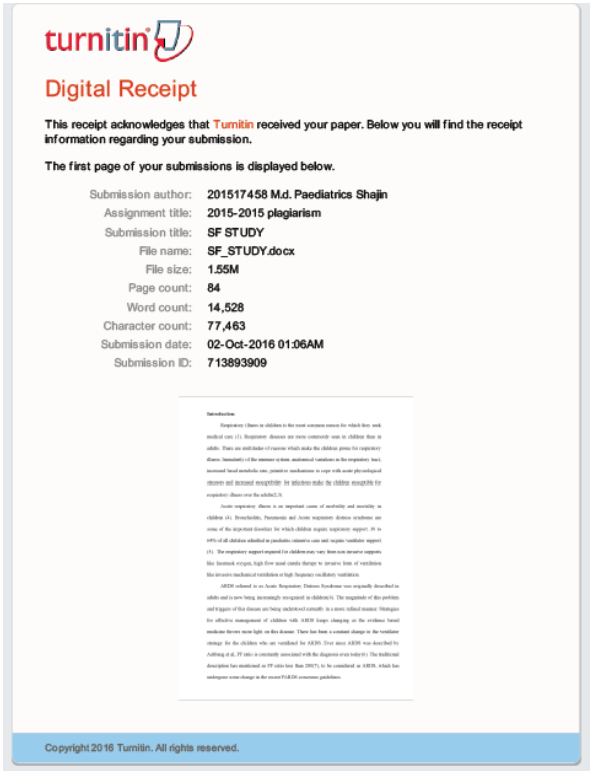
Contents

PLAGIARISM CERTIFICATE





INTRODUCTION

Respiratory illness in children is the most common reason for which they seek medical care(1). Respiratory diseases are more commonly seen in children than in adults. There are multitudes ofreasonswhich make the children prone for respiratory illness. Immaturity of the immune system, anatomical variations in the respiratory tract, increased basal metabolic rate, primitive mechanisms to cope with acute physiological stressors and increased susceptibility for infections make the children susceptible for respiratory illness over the adults(2,3).

Acute respiratory illness is an important cause of morbidity and mortality in children (4). Bronchiolitis, Pneumonia and Acute respiratory distress syndrome are some of the important disorders for which children require respiratory support. 30 to 64% of all children admitted in paediatric intensive care unit require ventilator support (5). The respiratory support required for children may vary from non invasive supports like facemask oxygen, high flow nasal canula therapy to invasive form of ventilation like invasive mechanical ventilation or high frequency oscillatory ventilation.

ARDS referred to as Acute Respiratory Distress Syndrome was originally described in adults and isnow being increasingly recognized in children(6). The magnitude of this problem and triggers of this disease are being understood currently in a more refined manner.Strategies for effective management of children with ARDS keeps changing as the evidence based medicine throws more light on this disease. There has been a constant change in the ventilator strategy for the children who are ventilated for

ARDS. Ever since ARDS was described by Ashbaug et al, PF ratio is constantly associated with the diagnosis even today(6). The traditional description has mentioned as PF ratio less than 200(7), to be considered as ARDS, which has undergone some change in the recent Pediatric ARDS (PARDS) consensus guidelines.

There are various parameters used in monitoring of children who are critically ill . Few of these parameters includes pulse oximeter saturation, Arterial blood gas, arterial blood pressure monitoring etc. Partial pressure of oxygen (PaO2) / Fraction (FiO2)of inspired oxygen, (PF ratio) a derived parameter from Arterial blood gas is used to diagnose and monitor the course of acute respiratory distress syndrome(8).

Children who are admitted in paediatric intensive care units are usually monitored round the clock using multi-channel monitors which includes pulse Oximetry(9). Oxygenation status plays a major role in the management of ARDS. Since the original description of ARDS in early 60's PF ratio has been used as a marker for the oxygenation status, which also has been changed in the recent PARDS consensus guidelines(10). While considering the oxygenation status, focus has now shifted from PF ratio to oxygenation index, as studies have proven that oxygenation index is good in predicting the mortality and outcome in ARDS(11), however the oxygenation index also will require PaO2 for its calculation.It is very cumbersome to perform the arterial blood gas in children as it requires multiple pokes, unless the child has an arterial line. Any reliable non invasive method would be an ideal technique to monitor the progression or

worsening of the lung disease. The need for an invasive procedure to determine PaO2 has led to an intensive search for an alternative method to monitor children with ARDS.

SF ratio appears as a response to the search of an appropriate alternative for monitoring children with ARDS(5). Pulse Oximetric Saturation (Spo2) / Fraction of inspired oxygen (Fio2) ratio (SF ratio) can be calculated easily, as we know both the variables. Various studies from abroad have shown a good correlation between the PF ratio and SF ratio(5,12,13). An American study done in children to compare the SF and PF ratio showed a good correlation between SF ratio and PF ratio(5). Similar observation was seen in the study done Iranian children(12). Although results from the above studies have shown that SF ratio can be used as a surrogate marker for PF ratio, the results varied in different centers. However data from Indian children are not available in this regard. Hence we have planned to do this study to compare and analyze the relationship between PaO2/FiO2 (PF) ratio and SpO2 /FiO2(SF) ratio in critically ill children requiring respiratory support (Invasive, Non-invasive ventilation & high flow oxygen device) in our PICU.

AIMS AND OBJECTIVES

Aims and Objectives:

AIM: To do a prospective observational study, comparing the relationship between Pao2/Fio2 (PF) ratio and Spo2 /Fio2 (SF) ratio in critically ill children requiring respiratory support in a Paediatric ICU of a tertiary care centre in South India.

OBJECTIVES:

1. To correlate the relationship between Pao2/Fio2 (PF) ratio and Spo2 /Fio2 (SF) ratio in critically ill children requiring respiratory support (i.e.: Invasive, non-invasive mechanical ventilation and high flow nasal canula therapy).

2. To determine the cut off value for SF ratio in relation to PF ratio to diagnose ARDS in our setting.

3. To analyze the relationship between Oxygenation index (OI) and Oxygenation Saturation index (OSI) in children with ARDS.

REVIEW OF LITERATURE

Burden of respiratory diseases in children:

Respiratory disorders are an important cause of morbidity and mortality in children. These disorders can be due to etiology of multifaceted origin and are the most common cause of under five mortality in the world. (14) Although various steps have been taken to tackle the respiratory diseases by different organizations like WHO, UNICEF, it continues to be a threat to the global health. Children are more prone for respiratory illness than adults for the following reasons:

- The lung development in children is not complete at birth. Up to two years of age, the proliferation of pulmonary capillaries and alveoli occurs and alveolar expansion continues beyond two years tilleight years of life. Hence, full development of lungs complete only by adolescence. During this period of life, children are more prone to the effects of air pollution and other environmental changes when compared to the adults, which puts them at a higher risk for respiratory illness(2).
- Moreover, the airways are narrower in children when compared to adults. As a result of which, the post inflammatory response in a child causes a significant obstruction which can be life threatening very rarely(2).
- When comparing with the adult population, the peripheral airways (i.e.) the bronchioles are smaller in infants. This leads in proportionately greater obstruction due to secretions/debris etc. Infants also have more mucous glands and they tend to have increased airway edema due to the less adherence nature of the airway mucosa.

- Children are more prone for hyperinflation and atelectasis of the lungs which is attributed to the fewer amount of interalveolar pores (Kohn's pores).This causes negative effect on the collateral ventilation thereby leading to hyperinflation and atelectasis.
- Airway edema is very dangerous in children than in adults. This is because 1mm of edema in the adult airway reduces only 19% of its diameter, whereas in infants, it reduces the diameter by 56%.
- The resting minute ventilation is double in infant (400ml/min/kg) when compared to that of an adult (150ml/min/kg).

The other supplementary reasons for increased respiratory morbidity in children include higher exposure to irritants because children spend more time in the outdoors and they inhale more pollutants, increased metabolic rate and oxygen consumption per kilogram bogy weight when compared with adults(3).

Overview ofGlobal epidemiology:

The causes of respiratory diseases in children can be broadly classified into infectious and non-infectious origin. Pneumonia is the number one cause of childhood mortality with approximately causing 1.3 million deaths per year.(15)Diseases due to infections play a major role in the underdeveloped nations whereas noninfectious causes predominate in the developed nations.

Respiratory infections in children:

Acute respiratory infections in children can be classified as upper respiratory and lower respiratory tract infections. These respiratory infections are not only limited to the respiratory tract but also have systemic syndrome which can manifest as SIRS (Systemic inflammatory response syndrome) due to reduced lung function and extension of infection, toxins into the systemic circulation. The examples are vaccine preventable diseases like diphtheria, measles and pertusis whichcan have both respiratory component and systemic component.

Upper respiratory tract infections:

Upper respiratory infections are commoner than lower respiratory tract. They include rhinitis, acute pharyngitis, acute tonsillitis, otitis media, sinusitis etc. Among these, pharyngitis and otitis can cause serious complications in children like acute rheumatic fever and deafness(16). The common organisms causing upper respiratory infections are viral which include rhinoviruses, respiratory syncytial virus, influenza, parainfluenza viruses, human metapneumo virus, adenovirus, coronavirus and so on. These infections are self-limiting most of the times. In few children, these viral infections can predispose to secondary bacterial infections of the sinuses and middle ear leading to lower respiratory infections.

Lower respiratory infections:

In children, the common lower respiratory infections observed are pneumonia and Bronchiolitis.

Pneumonia:

Pneumonia can be caused by both bacteria and viruses. Bacterial pneumonia is caused by organisms like Streptococcus pneumonia, Haemophilus influenza, staphylococcus aureus, and less commonly Mycoplasma pneumonia and Chlamydia pneumonia which cause atypical pneumonia(17). Viruses contribute to 40-50% of pneumonia in children. The common viruses causing infections in children include measles virus, Respiratory syncytial virus (RSV), Parainfluenza and influenza type A virus, and adenovirus.

The case fatality rate in developing countries among children with viral pneumonia is reported to be 1-7% (16–18), with bacterial pneumonia is 10-14 %, and with mixed pneumonia, it further rises to 16-19 %(17).

Bronchiolitis:

Bronchiolitis usually occurs in children less than three years. Bronchiolitis is commonly caused by viruses which include RSV, Human metapneumo virus, parainfluenza virus type 3 andInfluenza virus(17).

In special situations like infants with Human Immunodeficiency Virus (HIV) infection, children are prone for Lower respiratory tract infections, which can be caused by Pneumocystis jiroveci and cytomegalovirus which contributes to more than

50% of cases. The other organisms are gram negative bacteria, along with other super added infectionslike streptococcus pneumonia and staphylococcus aureus(19,20).

Another public health problem of significance is Tuberculosis in children. Infants and children are prone to develop more serious forms of Tuberculosis like disseminated Tuberculosis, Tuberculous meningitis etc(21). Diagnosis of TB in children is challenging because it is difficult to obtain sputum specimens in children. The laboratory tests to detect Tuberculosis in sputum are less likely to yield a positive result, even if the child has disease because children get the disease with small bacterial load (paucibacillary disease). These challenges could be overcome by attempting to diagnose Tuberculosis with the combination of the following:

- Clinical signs and symptoms suggestive of tuberculosis
- History of contact with Tuberculosis.
- Positive Mantoux test or positive IGRA.
- Chest X-ray with findings typically suggestive of TB.(42)

Non infectious causes of respiratory diseases in children:

The effects of industrialization, exposure to toxic substances and other environmental exposures are the key players which put the children in affluent nations into the risk of developing respiratory diseases(22). Children living next to the industries have got higher risk of respiratory problems related to the pulmonary interstitium(23). The other possible non infectious causes of respiratory diseases include near drowning,

trauma, toxic inhalation. Children who are getting admitted for post operative care following cardiac procedures and abdominal surgeries also tend to develop respiratory disease, secondary to blood transfusion, infections and other causes.

Adding to the burden of the disease is the emerging infectious diseases. Viral infections are emerging as new threat to our children. Newer strains of influenza viruses and other viruses like human Metapneumo viruses are recently found to be associated with increasing respiratory morbidity in children in addition to the older organisms(24).Increasing prevalence of respiratory diseases among children has globally impacted the medical community to extend the areas of research to decrease the knowledge gaps in children.

There has been a change in the trend of pediatric respiratory diseases, which has occurred in the past twenty years. There is a significant improvement in the diagnosis, monitoring and of course in the treatment of respiratory diseases. The improvement in treatment options also led to increased survival and increased morbidity in respiratory diseases. This change has increased the load for adult respiratory physicians as well. Many diseases once considered as the disease of children have now become the disease of adults too(23). The best example for this disease is cystic fibrosis, the screening, early detection and implementation of proper respiratory hygiene and exercises including the use prophylactic antibiotics whenever required, has increased the longevity of those children taking them into the adulthood(23). This improvement is equally supported by

the advancements in the genetic studies, by which the genetic mutations responsible for various diseases are identified, which helps in screening of those diseases in suspected children and also to an extent in confirming many respiratory diseases that has got underlying genetic mutations(25). The role of gene therapy to cure respiratory diseases is still in the experimental stage.

The relationship of active smoking with chronic obstructive pulmonary disease was a well established fact. The last two decades have explored the effects of passive smoking on respiratory diseases and especially, the exposure in the antenatal period has been linked with pre term births and respiratory morbidity in the early childhood(24). Another reason for this changing trend is the improved survival of pre term babies. Perinatal and neonatal care has achieved excellence in a way that babies born as early twenty seven weeks weighing as less than six hundred grams are surviving these days(23). This survival is associated with considerable morbidity at times. Respiratory morbidity in these babies manifests as Bronco pulmonary dysplasia, also termed as chronic lung disease of prematurity. The improved survival of these babies has led to the better understanding and improved definition of bronco pulmonary disease(26). Another breakthrough in the field of pediatric respiratory disease is the advent of newer antibiotics, anti-inflammatory molecules and monoclonal antibodies for various indications. The invention of Palivizumab, a monoclonal antibody against Respiratory syncitial virus, one of the most common causes for bronchiolitis has found to be a boon

in decreasing the recurrent bronchiolitis and upper respiratory tract infection in children with congenital acyanotic heart disease and also in pre term babies(27).

Overview of Indian epidemiology:

In Indian context, the situation is bit different.According to a report from World Health Organization (WHO), deaths due to respiratory disease in India are on the rise, accounting for about eleven percent of total deaths. India ranked first in the number of respiratory disease deaths with as many as 142 deaths per one lakhs population.(28)Ours is a large country with differences in religious, ethnic, socio economic and cultural parameters(29). Epidemiological mapping of respiratory diseases are very difficult in our nation due to the above mentioned factors, which are very variable in different parts of the country.Literature about the epidemiology of respiratory diseases in our country is limited, mainly owing to the sporadic and small studies that happens in different centers, which may remain unpublished and even in the available literature, there remains absence of uniform study designs, definitions and the methodology by which it is done.The Indian Council of Medical Research has formed a national asthma task force, under which a multicentric study including four centers viz Chandigarh, Kanpur, Delhi and Bangalore was done. This study found that female sex, advancing age, low socio economic status, history of atopy and family history of asthma are the risk factors for the development of asthma(29). This ICMR study has also highlighted that the incidence of chronic respiratory disease is on the rise in key cities of Andhra Pradesh, especially in Vijayawada and also in the neighboring districts of Guntur and West Godavari, owing to

the rise in vehicular pollution and smoking. According to the annual average data by Central Pollution Control Board, the average ambient air quality standards in those places were quite higher than the national average.(28)

There appears a great difference in the way, our pediatric critical care unit's functions when compared with those of developed nations. In United States of America, while establishing a pediatric intensive care setup, around 80% of the expenditure is spent for the personnel and the remaining 20% is for other expenditures including equipments.(30)But the reverse happens in developing nations like India; scarcity of resources and the increased population may be the reason for the same. The problem of availability and affordability play a major role in families with respiratory diseases. The spectrum of respiratory diseases in Indian children can be classified into congenital, infectious, inflammatory or autoimmune related and malignancies. India remains the global capital for tuberculosis and the spread of this disease is very rampant(31). Other respiratory diseases commonly encountered includeacute bronchiolitis, Pneumonia, Bronchial asthma and ARDS(32). Although there are various other respiratory diseases commonly encountered in children, the above mentioned diseases make the children present very sick to us. These children require care in pediatric intensive care units and they might as well require close monitoring.

Methods of respiratory support:

Children who are admitted in critical care units may require some form of respiratory support. This is given either by invasive or non invasive mode. The decision on the type of the respiratory support administered to each patient will be based on the clinical scenario.

Oxygen flow devices in children:

In children requiring respiratory support, oxygen can be administered through high flow or low flow delivery devices.

Low flow devices:

Low flow delivery devices include simple face mask, Nasal prongs (low flow), etc. In low flow systems, the flow is usually titrated on the flow meter and recorded in litres per minute. The fraction of oxygen delivered by low flow device and high flow device can be presumably obtained from the chart given below(33).

Oxygen device	Oxygen administered	FiO2 delivered
Nasal prongs	1 Litre /min	24%
	2 Litre/min	27%
	3 Litre/min	30%
	4 Litre/min	33%
Simple mask	6 -10 Litre/min	35-50%
Non –rebreathing mask	12-15 Litre/min	80-100%
Venturi mask	4 Litre/min	24-28%
	6 Litre/min	31%
	8 Litre/min	35-40%

High flow devices:

High flow delivery devices include Non re-breathing mask, Head box oxygen etc., through which the nearly 90-100% fio2 can be delivered.

Heated, humidified, high flow nasal cannula therapy (HHHFNC):

All high flow systems require humidification and the type of humidification device selected will depend upon the patient's requirements and the oxygen delivery system in use. Fisher and Paykel has designed a device called AIRVO, which has an inbuilt oxygen blender and humidifier to administer high flow oxygen in children requiring the same.

Non invasive ventilation:

Non invasive ventilation is a mode of respiratory support, where the ventilator support is delivered through the patient's upper airway using a mask or similar device bypassing the need for artificial airway like endotracheal tube or tracheostomy(34). The techniques used to deliver ventilation by NIV can be of two types, either a negative pressure ventilation or positive pressure ventilation (NIPPV)(34).

Non Invasive Positive Pressure Ventilation:

Ventilation can be achieved through an external interface like mouth piece, face mask or nasal prongs by using various ventilator modes like volume support, pressure support, bi level positive airway pressure (BIPAP), continuous positive airway pressure and so on(35).

CPAP:

Continuous Positive Airway Pressure (CPAP) is one type of non invasive ventilation which has gained importance in the recent past. The mechanism by which the CPAP acts is by maintaining the positive airway pressure which is at the set range throughout the respiratory cycle(34).

BIPAP:

In a respiratory cycle, two airway pressures used are inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). Bi-level positive airway

pressure has cycling between EPAP and IPAP. They deliver oxygen in two pressures one for inhalation and other for exhalation. This type of ventilation is used in neuro muscular disorders(34).

Indications for NIV in children(36)**:**

1. Impending fatigue of respiratory muscle,
2. Pneumonia,
3. Bronchiolitis,
4. Asthma,
5. Obstructive sleep apnea,
6. Chronic diseases like muscular dystrophy.

Contraindications for NIV(36)**:**

Absolute contraindications:

1. Respiratory arrest,
2. Uncooperative patients,
3. Trauma and burns involving face,
4. Air leak syndromes,
5. Apnea,
6. Decreased level of consciousness,
7. Any facial or upper GI surgeries.

Relative contraindications(36)**:**

1. Morbid obesity,
2. Anxious patients,
3. Excessive secretions.

Invasive ventilation:

In Invasive ventilation, the ventilator support is delivered through an endotracheal tube or tracheostomy. Invasive mechanical ventilation is nothing but artificial ventilation where the spontaneous breathing is assisted or replaced by the ventilator(37). Various modes used in mechanical ventilation are SIMV mode, SIPPV mode, ASV mode, APRV mode.

SIMV mode:

SynchronizedIntermittent Mechanical Ventilation is a variation of IMV, in which the ventilator breaths are synchronized with the patient breaths. SIMV mode is one of the weaning mode ventilation used in children.

SIPPV mode:

Synchronized Intermittent Positive Pressure Ventilation is a mode of ventilation in which the baby triggers to take a breath while the ventilator does the work of breathing. In this PIP/PEEP is adjusted to maintain adequate oxygenation and ventilation.

ASV mode:

Adaptive support ventilation is a type of positive pressure mechanical ventilation, wherein the frequency and the tidal volume of breaths of the patient are adjusted automatically based on the patient's needs.

High frequency oscillatory ventilation:

HFOV is a type of mechanical ventilation which maintains the recruitment of the lungs avoiding their over distension(38). In HFOV, tidal volumes of 1 to 4 ml/kg are delivered at high frequencies (3 – 15 Hz) with the help of an oscillatory pump. The main advantage is maintaining constant lung recruitment and avoiding lung injury which can be caused by over distension(39).

Indications of HFOV(39)**:**

1. In cases of oxygenation failure requiring FiO2 > 70% and PEEP > 14cms.
2. In cases of ventilation failure with pH <7.25 with tidal volume 6ml/kg and plateau pressure more than 30 cm of water.
3. In primary treatment of ARDS

Contraindications(39)**:**

1. Intracranial hypertension
2. Severe airflow obstruction.

ARDS in children:

ARDS refers to Acute Respiratory Distress Syndrome and it is one among the common cause of respiratory morbidity in children requiring acute care. ARDS was described as early as 1967 by Ashbaug et al from Ohio. The general prevalence of this disease was of very heterogeneous nature ranging from 9 – 16 cases per 1000 PICU admissions. (40). Indian studies estimates the prevalence of about 20/1000 admissions to PICU.(41) The overall mortality associated with this disease in general population is about 22%.(40)

Definition of ARDS in children:

ARDS is defined as a clinical syndrome of lung injury with hypoxic respiratory failure caused by intense pulmonary inflammation that develops after a severe physiologic insult. The disease process may be either a primary insult in which the disease process begins in the lungs, like in Pneumonia or it may be a secondary insult in which the lungs may be affected due to systemic disease process like sepsis or shock.(42)

Causes of ARDS in children:

There are various causes for the development of ARDS in children, the most important of which are mentioned hereunder.Causes of ARDS can be classified into diseases which cause direct lung injury and indirect lung injury. Pneumonia, Aspiration, near drowning, embolism are some of the causes of ARDS, which occurs by direct lung injury(10). Sepsis is the most common cause for ARDS, which occurs by indirect lung

injury and other least common causes in this category includes severe trauma and acute pancreatitis.(41)

Criteria to diagnose ARDS in children:

Initial definition of ARDS included the following criteria 1) $PaO_2/FiO_2 < 200$, 2) diffuse bilateral disease, 3)an identifiable insult like sepsis, aspiration or trauma within seven days of developing a compromise in oxygenation.(6) This definition was intended actually for adults as the definition included the term adults in it. In fact, it was during the American European Consensus Conference in 1994, the term Adults was replaced by Acute in the abbreviation of ARDS. Children have been characterized as Acute Lung Injury and ARDS based on the same definition. After a period of seventeen years, came the Berlin definition which devised significant changes including 1) Elimination of Acute Lung Injury and gradation of ARDS as mild, moderate and severe based on the disturbance in oxygenation, 2) Minimum requirement of 5cm H_2O PEEP to diagnose a case of ARDS and 3) the determination of cardiac failure was rendered more subjective. Pediatric Acute Lung Injury Consensus Conference was hence set up to define pediatric ARDS, specifically to look at its predisposing factors, causes and its pathogenesis(43). The other two objective of this conference included setting up of treatment goals for PARDS and to look at the priorities for future research in the field of ARDS. This consensus group had several meetings, before giving the final set of recommendations(44). The final draft had 151 total recommendations related to nine topics of PARDS studied by the consensus conference.

Excerpts from the new consensus recommendations from PALICC group(44)**:**

The salient points from the PARDS consensus conference are mentioned below.

- The new recommendations doesn't give any specific age group to diagnose ARDS, but it excludes lung diseases acquired due to perinatal lung insult or prematurity related lung disease along with other congenital lung abnormalities.

- The timing and triggers for ARDS continues to be the same, which is, the symptoms of hypoxemia and radiographic changes should occur within seven days of onset of clinical insult.

- Children with left ventricular dysfunction also can be diagnosed to have ARDS, if the acute hypoxemia and the chest findings cannot be explained by acute left ventricular failure or fluid overload.

- PF ratio (Partial pressure of oxygen/Fraction of oxygen administered was conventionally used to assess the level of lung disease severity. There was a change in the current consensus which goes on recommending Oxygenation Index (Mean airway pressure x Fraction of inspired oxygen) / Partial pressure of Oxygen over PF ratio in assessing the severity of lung disease in children with ARDS. However PF ratio continues to be the main parameter in diagnosing ARDS in children who are on non invasive ventilation likeCPAP (Continuous Positive Airway Pressure) and Bi PAP (Bi level Positive Airway Pressure).

- .Oxygen saturation index can be obtained by substituting oxygen saturation in the place of Pao2 while calculating oxygenation index. Oxygen saturation index (OSI) can be used instead of Oxygenation Index (OI), when OI is not available. Further to the above recommendation, it also states that SF ratio (Oxygen saturation/Fraction of inspired oxygen) can be used instead of PF ratio, when the later is not available to diagnose ARDS, especially in children receiving non invasive face mask ventilation with a minimum 5 cm CPAP.

- The recent PARDS recommendations has also defined ARDS in children with preexisting chronic cardio respiratory disease, provided they have the acute changes that fulfill the general criteria for ARDS.

- **Paediatric ARDS (PARDS)- Diagnostic Criteria**(44)**:**

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Diagnostic criteria for children at risk of PARDS:

<table>
<tr><td>Age</td><td colspan="3">Exclude patients with peri-natal related lung disease</td></tr>
<tr><td>Timing</td><td colspan="3">Within 7 days of known clinical insult</td></tr>
<tr><td>Origin of Edema</td><td colspan="3">Respiratory failure not fully explained by cardiac failure or fluid overload</td></tr>
<tr><td>Chest Imaging</td><td colspan="3">Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease</td></tr>
<tr><td rowspan="3">Oxygenation</td><td colspan="2">Non Invasive mechanical ventilation</td><td>Invasive mechanical Ventilation</td></tr>
<tr><td>Nasal mask CPAP or BiPAP</td><td>Oxygen via mask, nasal cannula or High Flow</td><td rowspan="2">Oxygen supplementation to maintain $SpO_2 \geq 88\%$ but $OI < 4$ or $OSI < 5$[1]</td></tr>
<tr><td>$FiO_2 \geq 40\%$ to attain SpO_2 88-97%</td><td>SpO_2 88-97% with oxygen supplementation at minimum flow[2]:
< 1 year: 2 L/min
1 – 5 years: 4 L/min
5 – 10 years: 6 L/min
>10 years: 8 L/min</td></tr>
</table>

Pathogenesis of ARDS:

The pathogenesis of acute respiratory distress syndrome has been studied for many years and there appears a lot of evolving concepts in the understanding of this disease. Lung endothelial injury and alveolar epithelial injury are thought to be the two most important factors in development of ARDS. Invariably, there will be a primary insult which triggers this whole process of the development of ARDS. The primary insult could be either sepsis or shock or other factors(45). The primary insult occurs mainly in the alveolo capillary unit and it leads in to development of acute phase which characteristically occurs within seventy two hours of the insult. (46) Following the primary insult there occurs accumulation of protein rich and neutrophilic fluid in the lung interstitium and also in the in the distal air spaces of lungs. There will be sloughing of the bronchial and alveolar epithelial cells. The accumulation of the protein rich fluid in the

alveolus causes inactivation of the surfactant. In the alveolar air space, alveolar macrophages secrete cytokines interleukin 1, 6, 8 and 10 along with tumor necrosis factor alpha(47). These cytokines causes chemotaxis and also stimulates neutrophils whichin turn release oxidants, proteases, leukotrienes and other inflammatory molecules like platelet activating factor. As a result of the above mentioned process, there occurs an increased capillary permeability and the normal endothelial barrier is lost(45). The role of platelets in the pathogenesis of ARDS continues to be a grey area. Although it was found initially that the platelet and vessel wall interaction cause more endothelial injury, recent studies has found the release of sphingosine 1 phosphate by platelets which appears to promote the endothelial function(45).

Investigators have found a difference between the mechanism of vascular endothelial injury and the lung endothelial injury. Mere endothelial lung injury, cannot lead to a complete ARDS picture unless it is associated with injury to lung epithelium. Animal studies have shown that administration of intravenous or intra alveolar endotoxin failed to produce alveolar edema because alveolar epithelium was intact(48). Alveolar edema developed in the same experimental model when there was instillation of live bacteria, which signifies that alveolar epithelial injury is must for the development of ARDS in addition to the endothelial lung injury. This significant epithelial lung injury is known to be caused by the neutrophils primed by their exposure to the chemokines. The neutrophils gain entry into the distal air spaces or alveolar epithelium by three stages. The first stage is the stage of adhesion, which occurs by adhesion of neutrophils into the

basolateral membrane by the help of β2 integrins. It was found that CD 11B and CD 18 help in this adhesion(45). Other factors that facilitate this adhesion include fucosylated glycoproteins and Junctional adhesion molecule (JAM-C). The second stage in this process is the neutrophil transmigration, during which these neutrophils crawl in between the epithelial cell membrane and this process was aided by CD47. Signal regulatory protein α (SIRP α) also helps in this transmigration process. Once they reach inside the cell, they enter into the third stage called stage of post migration causing the clinical manifestations(45).

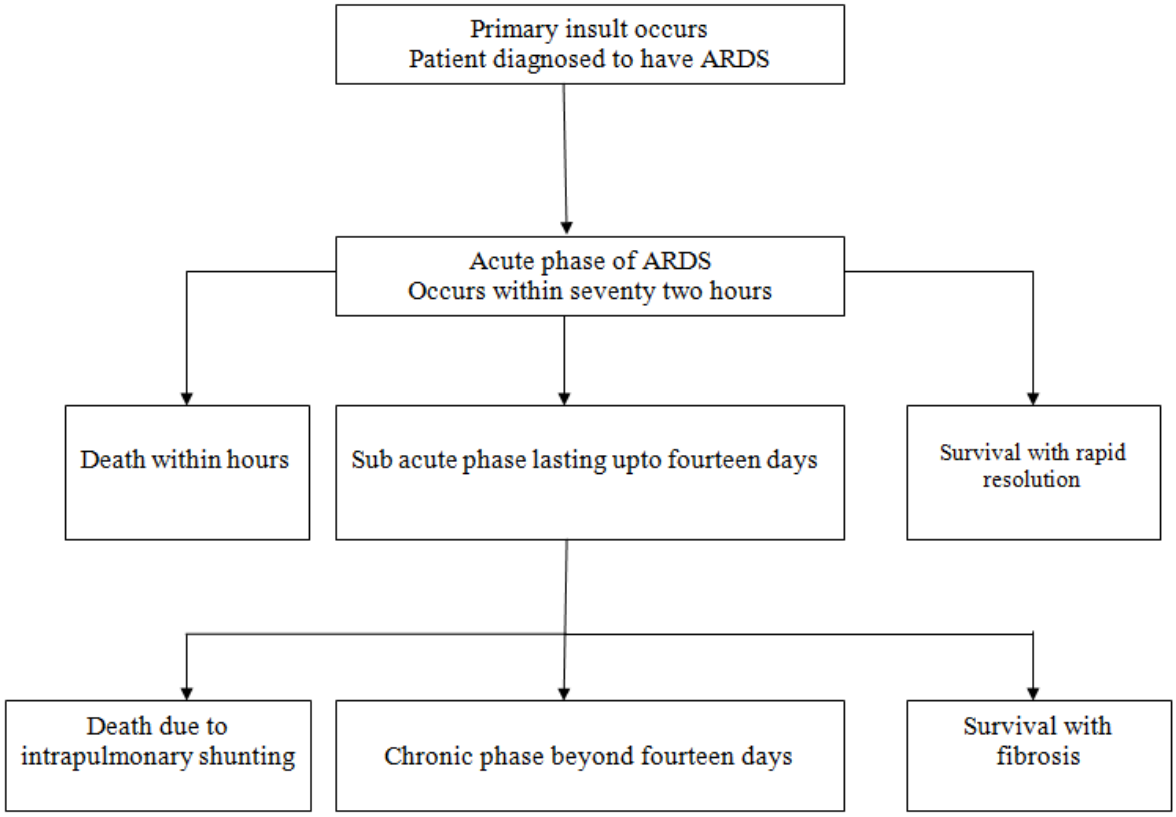
Pathological stages of ARDS(48)**:**

ARDS presents in children with breathing difficulty, with a very acute presentation. The clinical stages of Acute Respiratory Distress Syndrome are discussed hereunder.

The Acute phase usually lasts from first day to sixth day and it is characterized by interstitial and alveolar edema along with the presence of neutrophils in alveoli accompanied by characteristic endothelial and epithelial cell injury. The phase that follows acute phase is the sub acute phase which may last upto fourteen days, starting from a period of seven days from the onset of illness. Sub acute phase is characterized by the deposition of collagen along with proliferation of fibroblasts and type II epithelial cells. The chronic phase of ARDS occurs after fourteen days and the typical findings include alveolar macrophages and mononuclear cells. One could also see the resolution

of acute neutrophilic infiltrate and healing alveolar provided there is no persistent damage like ventilator associated lung injury. The main reason which delays the healing of ARDS is the impaired removal of alveolar epithelial fluid. The possible factors which contribute to this delay include alveolar epithelial injury, inflammation mediated injury to the ion transport machinery in the epithelial cells(48).

Natural course of ARDS(49)**:**



Predictors of ARDS in children:

Since the time of discovery of acute respiratory distress syndrome, a lot research has happened in the area of its prediction and prognostication. Immunocompromised state and multi system organ failure are considered as two independent factors which increase the mortality in children with ARDS(50). Duration of ventilation is another common outcome, which is related in predicting the ARDS outcome. The general rule is the more severe the ARDS, the more prolonged is the duration of days on ventilator. This factor can be complicated by other reasons including subglotic stenosis, decreased respiratory muscle tone, impaired secretion tolerance and so on(51). Ventilator free days are another factor considered as a predictor for ARDS outcome in children.

Bio markers in ARDS(52)**:**

The discovery of bio markers in ARDS is the recent advance in the field of ARDS. There are various types of bio markers which are identified as elevated among children with ARDS. The bio markers found to be beneficial in children can be obtained from the blood or from the bronco alveolar fluid. The various types of bio markers may be related to markers of inflammation, coagulation and necrosis, epithelium related markers and markers related to endothelium. Few bio markers are also found to be associated with surfactant proteins, other proteins and there are some non protein bio markers as well.

Blood derived bio markers:

The most important biomarkers associated with ARDS are discussed here under. Friedman et al did a study on essential fatty acids and prostaglandins in the babies with acute respiratory distress syndrome and found that prostaglandin F was elevated in children with respiratory distress syndrome mainly due to decreased PGE to PGF ratio. Other protein bio markers like aquaporin, B type natriuretic peptide, sFAS-L, sST2 were also being studied. Aquaporin – 5 was elevated in neonatal respiratory distress syndrome and it correlated well with the disease severity(52). Researchers have also found that B type natriuretic peptide was increased in children with ARDS who are on prolonged mechanical ventilation with worse hypoxia. Surfactant proteins A, B and D are the surfactant proteins, which are elevated in children with ARDS. Various endothelial associated factors also behave like bio markers in children with ARDS. Angiopoietin-2, soluble E selectin, endothelin – 1, Soluble thromboplastin and von willebrand factor are some of the vascular endothelial bio markers which tend to get elevated in children with ARDS. Epithelial derived bio markers which are elevated in ARDS include soluble intercellular adhesion molecule – 1 and krebs von den lungen - 6. Anti thrombin III is typically found to be decreased in children with ARDS. Interleukins 1, 4, 6, 7, 8, 10, 12, 13 are also found to be elevated in children with ARDS(45).

Bio markers from Bronco alveolar fluid:

There are similarities in the bio markers obtained from the blood and bronco alveolar fluid. Some markers can be exclusively isolated from the bronco alveolar fluid alone in contrast to some, which can be obtained from both blood and bronco alveolar fluid. MMP (Matrix metallo proteinase 8 and 9), MPO (Myeloperoxidase) and TIMB (Tissue inhibitor of metalloproteinase 1 and 2) are some of the bio markers which are found to be elevated in the bronco alveolar fluid of children with ARDS. Soluble receptor for advanced glycation end products is basically a protein, which can be seen in the basolateral membrane of type I pneumocyte and is found to be elevated in ARDS. This was available predominantly from the adult data and it was also found to be correlated with increased mortality, organ failure and decreased alveolar fluid clearance(52).

Monitoring of children with ARDS:

Monitoring of children admitted in pediatric intensive care units, especially the children, who are on respiratory support forms the cornerstone in management of respiratory diseases. The science of monitoring critically ill children has started way back and was very much linked with the development of pediatric critical care as a specialty(53). The first pediatric intensive care unit was established in Europe during 1955 by Goran Haglund at children's hospital in Sweden(54). Ten years later Cheston Berlin developed pediatric intensive care unit at children's hospital in Columbia. Subsequently, the field of pediatric intensive care started blooming globally contributing a significant extent in the monitoring of sick children.Guidelines on monitoring critically

ill children on respiratory support were initially given by Society of Critical Care Medicine (SCCM), which were predominantly adult based guidelines(30). Formation of various pediatric study groups and societies lead to the development of protocols to monitor critically ill children on respiratory support and this in turn has led to the discovery of machines and gadgets, enabling us to monitor these children more effectively(53).

Monitoring of children in pediatric intensive care unit may include invasive and non invasive methods. Various parameters which help in monitoring these childrenincludemonitoring of the vital signs – the blood pressure, heart rate, respiratory rate, saturation which can be donecontinuously by a pulse oximetry. Another vital parameter is capillary refill time, which requires the presence of a person to monitor. Other parameters used in the pediatric intensive care units for monitoring are end tidal carbon di oxide, intra cranial pressure, arterial oxygen saturation, measurement of intra abdominal pressure and so on(53).

Saturation monitoring in children:

The use of oxygen saturation for monitoring children with respiratory distress dates back to 1864, when George stokes discovered that oxygen in the blood was transported by a colored component; however it was on 1935, that Karl Mathews developed the first system to measure oxygen saturation by transillumination(9). The next generation saturation monitor was based on spectrophotometry and subsequently in

1980’s, the non invasive pulse oximeter’s came into existence to monitor the oxygen saturation.

Saturation monitoring in children has played a major role in monitoring children who are on respiratory support. One major reason for this is because; the clinical assessment of hypoxemia cannot be relied on, as it can be altered by many factors including hemoglobin concentration, tissue perfusion and skin complexion. The widespread application of oxygen saturation measurement has made it to be considered as the fifth vital sign. The main principle behind the oxygen saturation measurement is based on the different characteristics of oxygenated and deoxygenated hemoglobin and its relation to red and infrared spectrum(55). It has been found that the deoxyhemoglobin has got more red light absorption at the wave length of 600 to 750 nm, on the other hand, oxyhemoglobin has got more infrared light absorption at the wave length of 850 to 1000 nm. The percentage of oxyhemoglobin will be calculated by obtaining the ratio of lightabsorption in the red and infra red spectra(9). A plethysmographic wave is obtained from the microprocessor inside the device and saturation is calculated from the absorption ratios with the help of an algorithm stored in the micro processor of the device.

Limitations of saturation monitoring(9)**:**

Motion artifact is one of the limitations of the pulse oximetry, which could be identified by the distorted plethysmographicwave form. New generation saturation

monitors are made in such a way to counter this limitation. Low perfusion states like shock, hypothermia and other factors like application of blood pressure tourniquet was once considered as confounders in measuring the exact saturation. Advances in the field of bio engineering have helped to tackle this by the invention of new generation equipment with signal extraction algorithms, helping them to work well at low perfusion states. The presence of a normal plethysmographic waveform reassures us the correctness of the saturation. Other theoretical factors including skin pigmentation, nail polish and bilirubin levels, once thought to affect the pulse oximetry value has now been addressed with the advent of new devices. Improper positioning of the probe, particularly inappropriate size of the probes can be a cause of erroneous saturation values, which has to be addressed appropriately(9). Anemia, once claimed to affect the accuracy of the saturation value has been disproved now, however in children with severe anemia with hemoglobin less than 5gm%, there can be a change in the saturation values. In contrast, it has been proven that saturation values will not be affected by polycythemia. Saturation readings should be measured with caution in children with abnormal hemoglobin molecules like carboxy hemoglobin and in also in children who are treated with methylene blue(56).

Other uses of Pulse oximetric saturation monitoring:

The most important other uses of saturation monitoring include its application in monitoring hospitalized children. Intermittent monitoring is preferred over the continuous monitoring in stable hospitalized children. Monitoring also helps us to decide the need of

supplemental oxygen therapy. Another use of saturation monitoring is during neonatal resuscitation. It also plays a major role in screening of neonates for congenital heart diseases(9).

Paediatric Index of Mortality 2 scores:

Mortality risk prediction models are important tools in the assessment of care in ICUs. Paediatric index of mortality score is one among the different risk scores which are used to rate the severity of medical illness for children admitted in ICU(57). It is designed to predict the mortality of a patient in a systematic manner. In 2003, Salter et al gave a modified version of PIM2 SCORE which is used currently. Ideally,this score should be calculated at the time of ICU admission(58). This score uses various coefficients likesystolic Blood Pressure, base excess from arterial blood gas, Fraction of inspired oxygen, Partial pressure of oxygenfrom the first arterial blood gas and so on.Salter et al has validated these variables in the calculation of this risk score. It is being hypothesized that all these variables should be collected from the patient in the first face to face contact between the patient and the ICU clinician, which can occur at any time either at the time of ICU admission or in the casualty or while in the ward, when being assessed by the ICU clinician prior to ICU admission. In certain situations, due to practical problems, the values are considered even till first hour of admission.

Variables used in PIM2 scoring(57–59):

- Systolic Blood Pressure:

  Scoring will be done as follows.

  120, if the value is unknown,

  0, when the patient is in cardiac arrest,

  30, If the patient is in shock andwhen the BP is not recordable.

- Pupillary(60) reaction to bright light:

  It is used as an indicator for brain function. Pupillary reaction will not be recorded, if the patient is under the influenceof certain drugs or toxins.

  If the pupils are >3 mm and both fixed the score is 1,

  All other circumstances the score is 0.

- Partial pressure of Oxygen (PaO2):

  The PaO2 will be taken as the score

  If the PaO2 is unknown, then the score is zero.

- Fraction of Inspired Oxygen (FiO2) at the time of PaO2 entry:

  The FiO2 will be taken as the score

  If the FiO2 is unknown, then the score is zero.

- Base excess in arterial blood:

  The base excess will be taken as the score

  If the base excess is unknown, then the score is zero.

- Mechanical ventilation:

  This variable looks at mechanical ventilation during the first hour of ICU admission. This is entered either as yes (score – 1) or no (score -0).

- Elective admission to ICU:

  Elective admission to ICU denotes that if the admission can be delayed for six more hours. This variable again is entered as either ‘yes’ or ‘no’.

- Recovery from surgery is the main reason for ICU admission?

  This variable is also entered as ‘yes’ or ‘no’. These procedures include, post laparotomy, cardiac catheter insertion or any other radiological procedure.

- Reason for ICU admission following post cardiac bypass?

  This variable is scored as ‘yes’ or ‘no.’

  In all the above variables, No indicates score 0 and Yes indicates score 1

- High risk or Low risk diagnosis?

  High risk conditions include,

  1. None – Scored as 0
  2. Cardiac arrest preceding ICU admission- Scored as 1
  3. Severe combined immune deficiency – Scored as 2
  4. Leukemia or lymphoma after first induction Scored as 3
  5. Spontaneous cerebral hemorrhage- Scored as 4
  6. Cardiomyopathy or myocarditis – Scored as 5

7. Hypo plastic left heart syndrome (Corrective surgery done in the neonatal period)- Scored as 6
8. HIV Infection- Scored as 7
9. Liver failure -Scored as 8
10. Neurodegenerative disorder – Scored as 9

Low risk conditions include:

1. None - Scored as 0
2. Bronchial asthma – Scored as 1
3. Bronchiolitis - Scored as 2
4. Croup- Scored as 3
5. Obstructive sleep apnea- Scored as 4
6. Diabetic ketoacidosis- Scored as 5.

Once, all these variables are collected,the total score will be computed.

The risk score is calculated asfollows(61):

PIM2 score = -0.9282(Elective) - 1.0244(Recovery) + 0.7507(Bypass) + 1.6829(High-Risk) - 1.577(Low-Risk) + 3.0791(Pupils) + 1.3352(Ventilator) + 0.01395(absolute value of SBP-120) + 0.1040(absolute value of base excess) + 0.2888(100 x FiO_2 / P_aO_2) - 4.8841

Risk of mortality = e ^ (PIM2 score) / [1 + e ^ (PIM2 score)]

Revisions in the PIM2 Scoring system(57)**:**

- The first version of Paediatric Index of Mortality (PIM) scoring system was initially developed in the Australian PICU units, of which the scoring model included data from eight units and included only 5900 admissions. The revised PIM2 scoring model included data from 14 PICUs from different countries including from Australia, United Kingdom, and New Zealand.

- Three variables namely, admitted for recovery from surgery, admitted following cardiac bypass and low risk diagnoses were included in the revised version.

- In the high risk diagnosis category, following changes were made:

Changes in the criteria used for cardiac arrest, inclusion of liver failure as a high risk diagnosis and omission of IQ below 35 from the high risk category. The analysis of the PIM2 model has put forward that assessing the IQ proved to be difficult in coding particularly in young children. Moreover, they added that avoiding the IQ variable altered their AUC of ROC graph by 0.1%.

Performance of PIM2 Scoring system(59)**:**

Salter et al in his prospective study in revising and updating the PIM2 scoring involved 14 PICU's with 21,529 admissions. The new PIM2 model better discriminated children between death and survival, the AUC in the ROC curve was found to be 0.89-0.92.

Advantage of PIM scoring system compared to other scoring models:

The source of data in PIM scoring system is the admission data where as in most of the other scoring systems, the data is 12-14 hours old data. The advantage of using the admission data is, that the data will not biased by the further treatment provided.

Disadvantages' of PIM2 Scoring system:

Studies document that PIM2 over predicted the mortality risk in PICU between 2010 and 2011. Revising few variables like inclusion of liver failure, omission of liver function although improved the outcome of the risk model, few variables like cardiac bypass, low risk diagnosis categories did not predict the mortality risk. Hence, in order to overcome all this shortcoming, PIM3 is being constructed which has further revised few variables(62).

Arterial blood gas monitoring in Pediatric Intensive Care Units:

Pulse oximetry and End tidal Co2 were considered as the two important parameters to continuously monitor the sick children admitted in pediatric intensive care units. Each has its own advantages and disadvantages. Pulse oximetry is affected by change in the probe position, movements in the probe and during the movements of the limb. The End tidal Carbon di oxide has its own disadvantages as it's affected by different forms of pulmonary pathology and it was also found to be unsuitable in children who are on high frequency oscillatory ventilation. The invention of arterial blood has led to a significant level of improvement in monitoring of children, who are admitted in pediatric intensive care units(60). The arterial blood gas gives the partial pressure of

oxygen and carbon dioxide in the arterial blood.The other important aspect of arterial blood gas is its rapidity in which it produces the results. When the blood sample is fed to the machine, the analysis happens within few minutes and the results are ready. Another added advantage with arterial blood gas lies in its capability to find the values of other derived parameters like electrolytes, glucose and lactate levels.

The first blood gas analyzer was developed in 1957 by John Severinghaus, which originally measured pH, pCo2 and pO2. Blood gas analyzers came to the market during mid 60's(53). It was on 1985, the combined blood gas analyzer with electrolyte analyzer came into the practice.Since then a whole lot of advancements had occurred in this arterial blood gas machine. Currently running a blood gas will help us to obtain various details including pH, pO2, pCo2, sodium, potassium, chloride, ionized calcium, ionized magnesium, glucose, lactate, urea, hematocrit, hemoglobin, oxygen saturation. Such a useful investigation is definitely well suited for the monitoring of children who are admitted in critical care units, as it gives a lot of information in a single context. Recent advance in the field of arterial blood gas monitoring is the invention of continuous arterial blood gas monitoring(60). A sensor will be placed through the 20 gauge arterial catheter which helps in continuous measurement of arterial blood gas values. The sensor is a single small device measuring about 0.48 mm, which consists of the following parts including an opto chemical pH and pCo2 detector that changes the color in response to the change in pH and pCo2 respectively, a Clark oxygen electrode that detects the partial pressure of oxygen and a thermocouple to measure the temperature differences. This

sensor is kept inside a Y connector tubing which allows the pressure monitoring, withdrawal of blood samples. The results of the measurements are continuously displayed on a screen. The main advantage of this monitor is that it avoids multiple withdrawals of blood samples and also it gives the trend of different variables over the past twenty four hours.

Another important application of arterial blood gas is to diagnose children with Acute Respiratory Distress Syndrome. ARDS was diagnosed traditionally using the PF ratio which was calculated by Partial pressure of oxygen (paO2) which was obtained from the arterial blood gas divided by the Fraction of inspired oxygen. PF ratio less than 300 was considered as acute lung injury and PF ratio less than 200 was considered as ARDS. Though the guideline was brought out mainly for the sake of adults, this was being practiced for many years to diagnose ARDS in children(63).

Having discussed the various advantages of the arterial blood gas monitoring, it is also important to note the unfavorable effects of arterial blood gas monitoring. The major disadvantage with the arterial blood sample is the need for arterial puncture. Arterial puncture is associated with increased risk of infections, hematoma formation, bleeding from the site of puncture and occasionally feeling of giddiness in some children(64). Peripheral nerve damage can occur in very rare instances. Availability of arterial blood analyzers remains another challenge for the use of arterial blood gas in routine

monitoring. Many resource limited settings may not have the opportunity to have an arterial blood gas analyzer.

These drawbacks with the arterial blood gas have favored the saturation monitoring and have given an impact to the concept of saturation monitoring again. The milestone in the monitoring of saturation is the inclusion of SF ratio for the diagnosis of PARDS(44). SF ratio is obtained by the oxygen saturation divided by the fraction of inspired air(65).

PF ratio in children:

PF ratio, which is the ratio of partial pressure of Oxygen to the fraction of inspired oxygen, is widely used as an indicator of hypoxemia(66). PF ratio is used as one of the criteria in the diagnosis of ARDS according to Berlin's definition(67). Based on the degree of hypoxemia ARDS is sub classified as follows:

Mild : P/F ratio >200 but <300 with PEEP/CPAP >5cm H20.

Moderate : P/F ratio >100 but < 200 with PEEP >5cm H20.

Severe : P/F ratio <100 mmHg with PEEP >5 cm H20.

There can be variations in the PF ratio in relation to the altitude.

Advantages of PF ratio(66)**:**

1. PF ratio calculation is quick and simple.

Disadvantages of PF ratio:

1. PF ratio is inversely proportional to barometric pressure.

2. PF ratio is an indicator of hypoxemia but it cannot differentiate the cause of hypoxemia which can be either due to alveolar hypoventilation or other causes which cause hypoxemia such as ventilation perfusion mismatch.

3. It is dependent on the FiO2 due to the influence of the Oxygen hemoglobin dissociation curve.

SF ratio in children:

Although we have reached the stage to discover bio markers from the concept of monitoring children with ARDS by means of pulse oximetry, there seems to be an inadequacy in the non invasive monitoring of childrenwith ARDS. Though the advent of bio markers in ARDS appears to have a promising role in diagnosing and predicting the development of ARDS, a lot more need to be studied and proved before it is brought to the bedside practice(52). At present, of all the ways available and discussed, the monitoring of arterial blood gas appears to be the most beneficial tool to diagnose and monitor the children with ARDS. Each modality has its own pros and cons, which has to be weighed in the context of the clinical setting. Arterial blood gas monitoring lies superiorwhile comparing all the modalities available for diagnosis and monitoring of children with ARDS.

The arterial blood gas monitoring, though, it was found to be the ultimate in monitoring of children with ARDS, has its own limitations. The most important disadvantage will be the innumerable arterial punctures, which the child has to go through, during the course of treatment for ARDS. When researchers started searching for an alternative, the monitoring of saturation appeared reasonable. Soon, there were studies looking at the appropriateness of saturation, to be used as an alternative to arterial blood gas monitoring for the children with ARDS. SF ratio (Saturation/Fraction of oxygen inspired air) was identified and studies were aimed at finding the correlation between the SF ratio and PF ratio in the setting of ARDS(65).

An American study done in children to compare the SF and PF ratio showed a good correlation between SF ratio and PF ratio. In addition, this study also brought out the cut off SF ratio to diagnose Acute Lung Injury as 263 and to diagnose ARDS as 201, for the corresponding PF ratio of 300 and 200 respectively(68). They observed that thesensitivity and specificity to diagnose ALI using SF ratio was 86% and 47% respectively and to diagnose ARDS was 68% and 84% respectively(69). There was yet another study done among Iranian children which brought out an SF ratio cut off of 235 to diagnose ALI and 181 to diagnose ARDS(70). In this study, they demonstrated 57% sensitivity and 100% specificity to diagnose ALI and 71% sensitivity and 82% specificity to diagnose ARDS(71). United states critical illness and injury trials group did a study and found that SF ratio obtained within six hours of the admission can be used as an

independent predictor for development of ARDS in children who are at risk.(72) The median SF value in a patient who developed ARDS was 254 and in a patient who did not develop ARDS were 452. They have also found that there was a significant association between the SF ratio and ARDS. SF was found to predict ARDS in a dose dependent manner. SF ratio less than 100 had an odds ratio of 2.49(1.69 – 3.64, P <.001) and SF ratio 100 - 200 had an odds ratio 1.75(1.16 – 2.58, P = .007), while SF ratio 200 – 300 had an odds ratio of 1.62(1.06 – 2.42, P = .025).

Neal et al had tried to define acute lung disease with the help of oxygen saturation index(73). Oxygen saturation index is the product of mean airway pressure and fraction of inspired oxygen divided by the partial pressure of oxygen. They found that SF ratio cut of 253 and 212 equaled with the criteria for PF ratio less than 300 and 200 suggesting acute lung injury and acute respiratory distress syndrome respectively(73). Further to this they also looked at the correlation between ARDS and oxygenation index, from which they concluded that oxygenation index of more than 5.3 and 8.1correlated with acute lung injury and ARDS respectively. Having said the good correlation between oxygenation index in diagnosing ARDS and acute lung injury, one should also note that oxygenation index again requires arterial blood gas to find out the PaO2 (Partial pressure of oxygen). To avoid this difficulty, they have used oxygen saturation index in diagnosing ARDS and acute lung injury, wherein they found that 6.5 and 7.8 as the OSI cut off to diagnose acute lung injury and ARDS respectively(43).

Although, most of the studies mentioned had looked at the SF ratio cut off for PF ratio less than two hundred and three hundred, in an attempt to diagnose acute respiratory distress syndrome and acute lung injury, the recent PARDS consensus conference had set the PF ratio cut off as 300 in children who are on non invasive ventilation. In children who are on mechanical ventilator, the current evidence states that oxygenation index has got more accuracy in diagnosing ARDS than the PF ratio. In the same way, the PARDS consensus conference had set the cut off oxygenation index which goes on as follows. Mild ARDS in children with oxygenation index more than 4 and less than 8 and moderate ARDS in children with oxygenation index between 8 – 16 and severe ARDS in children with oxygenation index more than sixteen(44).

All the studies quoted above have shown that SF ratio can be used as a surrogate marker for PF ratio but there appears a variation in the results among different centers. Moreover, studies from our country are not available. In view of the variations noted in the different studies, it is of paramount importance to look and prove the correlation of SF ratio and PF ratio in Indian children and it is also necessary to set a cut off SF ratio to diagnose ARDS in our population.

The scarcity of Indian literature and paucity of Indian studies along with the need to establish a cut off ratio for Indian children is the reason to undertake this study.

MATERIALS AND METHODS

Study design and setting:

This isa prospective observational study done in the Paediatric intensive care unit of Christian medical college, Vellore. Christian medical college is a quaternary care centre with 2800 beds catering to the medical needs of people of India and neighboring countries. Paediatric Intensive care unit at CMC has eleven beds with a thirteen bedPediatric high dependency care unit attached with it. PICU receives patients from Paediatric Emergency, Paediatric wards and also from operation theatres for post operative care. The study was done for a time period of seven months from February to August2016.

Statistical methods:

Data were summarized using mean (S.D) and median (IQR/range) for continuous variables and frequency (percentage) for categorical variables.Independentt‘test /rank sum test were used to compare continuous variables. Chi square test was used to find the relation between SF ratio and PF ratio and other categorical variables.To find the discrimination cut off of SF ratio, the PF ratio grouped for 300 and 200 was used as outcome and an ROC analysis was done. The diagnostic accuracies were presented for the determined cut off with 95% CI.A linear regression was done having SF ratio as outcome and PF ratio as exposure to predict change of SF ratio with each unit of PF ratio. All the statistical methods were done using STATA/1C 13.1.

For all the analysis significance was kept at 0.05 levels.

Sample size:

The sample size was calculated using the following formula:

$$n = 4pq/d2$$

Where p: Specificity available from the previous studies

q: 100 – p

In the reference study we have taken, the specificity is 84%,

p stands for specificity available from a previous study(68).

d stands for precision which is 5,

Therefore the sample size will be

4x84x16/25 = 215

Inclusion criteria:

1) All children who needs oxygen supplementation and requiring respiratory support – either invasive, non-invasive mechanical ventilation or high flow nasal canula therapy

2) Children with ARDS (Diagnosed based on PARDS criteria) requiring invasive mechanical ventilation /non-invasive ventilation

Exclusion criteria:

1) Children with suspected or probable Congenital heart disease or any anatomic anomalies of lung,

2) Children with Chronic Lung disease,

3) Children diagnosed to have conditions like Methaemoglobinemia,

4) Children (parents) who decline to give consent to participate in the study.

Methodology:

Children admitted in PICU, who fulfilled the inclusion criteria, are recruited after obtaining the consent to take part in the study.At the time of admission, when the first arterial blood gas is done, Pao2 and Spo2 are measured simultaneously and these will be documented in the standard proforma. The Fractional inspired oxygen (FiO2) which is administered to the patient at that point will also be documented. A second sample was done when the participant deteriorates needing escalation of respiratory support or 24 hours after admission, whichever is the earliest. The PF ratio and SF ratio was calculated using the documented variable – SpO2, FiO2, PaO2 and analyzed to correlate the relationship.

Receiver Operator Characteristics (ROC) curve shall be constructed and area under curve (AUC) measuredto find out the cutoff value of SpO2/FiO2 (SF) ratio and Oxygenation saturation index.

The Oxygenation Index (OI) and Oxygenation Saturation Index (OSI) are calculated as follows,

$$OI = \frac{MAP \times FiO2}{PaO2}$$

$$OSI = \frac{MAP \times FiO2}{SpO2}$$

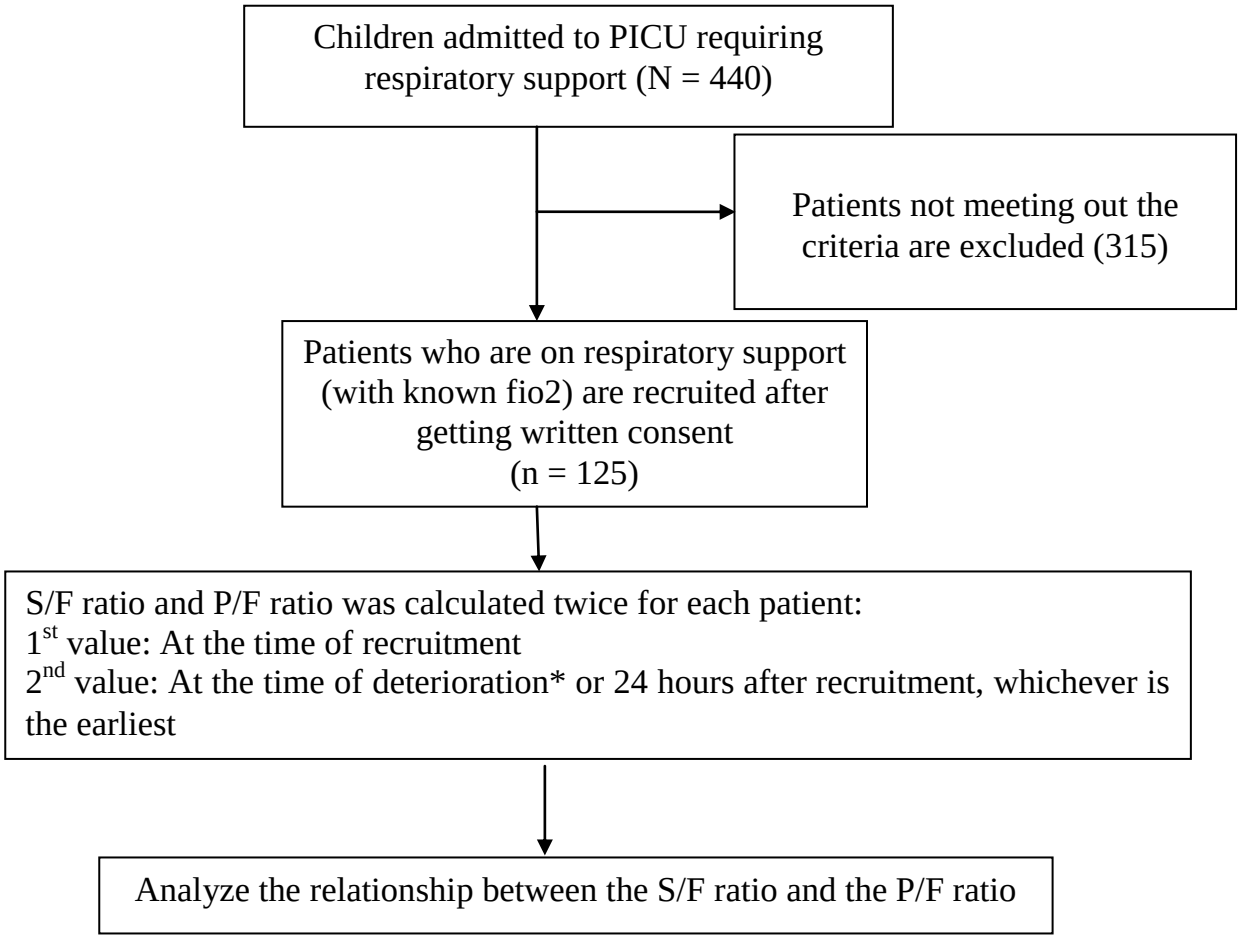
MAP: Mean airway pressure (in ventilated patients)

Paediatric ARDS (PARDS)- Diagnostic Criteria(44)

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Detailed diagrammatic Algorithm of the study:

Flow chart 1:



* - Deterioration is defined as the requirement of higher form of respiratory support.

RESULTS

Demographic details:

Our study had total of one hundred and twenty five children recruited during the entire study period of seven months. Two arterial blood gases from each patient were taken for our study with corresponding Pao2 and Spo2. The baseline characteristics of our study population are as follows.

Age:

The median age of our study group was 8 years. The minimum age of our study participant was one month and the maximum age was fifteen years. We analyzed them under three sub groups according to their age namely 28 days to one year, one to five years and six to fifteen years. We had almost equal number of children in all three groups.

Table 1:Distribution of study population according to age group and ARDS

Age	**Total No. %**	**Children with ARDSNo. %**
<1 year	36 (28.8%)	7 (19.4%)
1-5 years	42 (33.6%)	5 (11.9%)
6-15 years	47 (37.6%)	15 (31.9%)

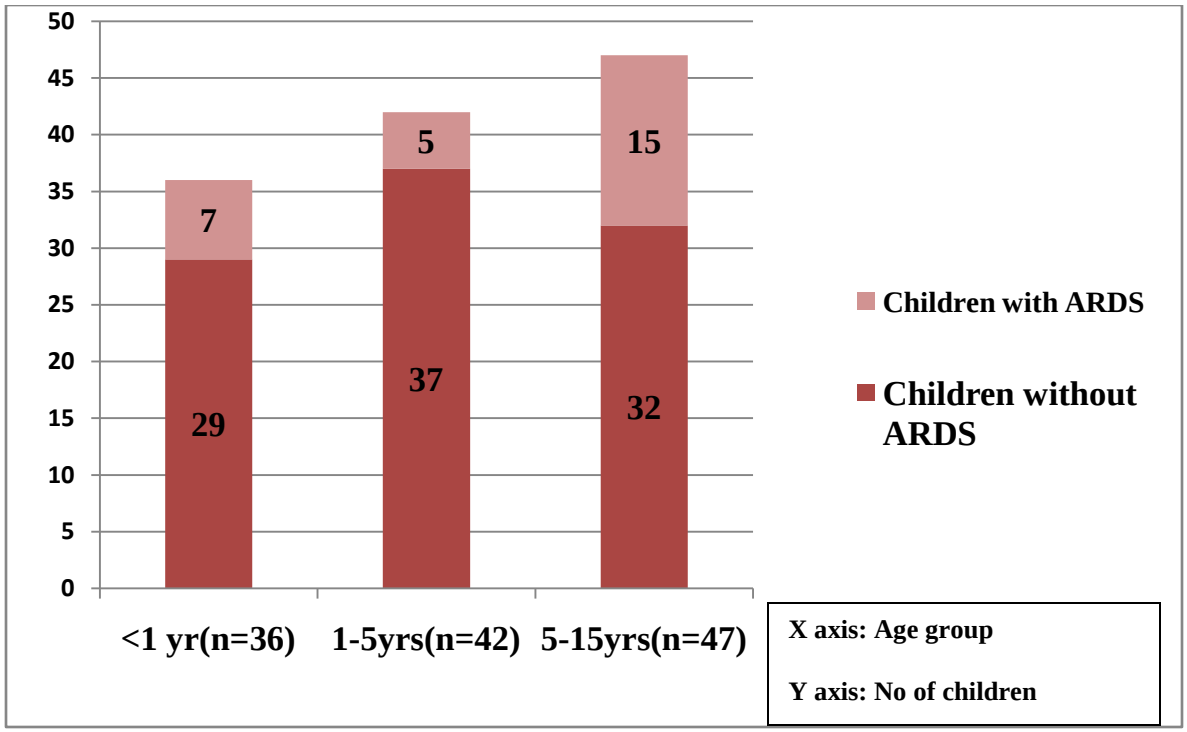


Figure 1:Total number of children and children with ARDS based on age group

Sex:

Among the one hundred and twenty five children recruited, eighty three children were male (66.4%), of which sixteen had ARDS and six of them expired due to ARDS. Forty two children were females (33.6%) in the total study group, among them eleven of them had ARDS and four girls succumbed to the illness.

Table 2: Distribution of sex in our study population

Sex	**Number**	**Percentage**
Male	83	66.4%
Female	42	33.6%

Table 3: Distribution of ARDS and their mortality based on their gender

Sex	Total ARDS	Expired
Male	16 (59.25%)	5
Female	11(40.74%)	4

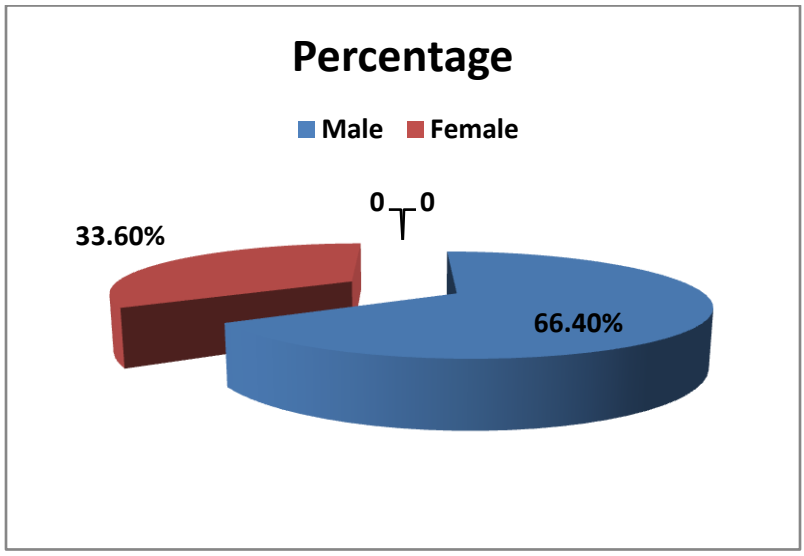


Figure 2:Pie diagram showing the sex distribution in our study population.

The mean PF ratio observed among the boys was 307.64 +/- 158.74 and among the girls were 299.6 +/- 139.06. The mean SF ratio observed among the boys was 213.62 +/- 57.76 and girls were 211.69 +/- 56.12. There was no statistical significance observed on comparison of ratios with gender. SF ratio Vs gender (p value: 0.8403) and PF ratio Vs gender (p value: 0.9059).

Primary diagnosis in children:

CNS diseases (Acute CNS infection) are the most common indication for admission into our Paediatric intensive care unit. Status epilepticus is the most common presentation among the type of neurological diseases. Children with global developmental delay and symptomatic generalized epilepsy also constituted a significant number among the children who presented with seizures. Many children who presented with seizures required ventilator support either for neuro protection or for poor sensorium. They constituted 15.2% of the total study group.

Sepsis with organ involvement (cardiovascular or respiratory) was the second common reason (12%) for which children received critical care support. The different ways by children with sepsis presented included shock, ARDS or acute kidney injury and the mortality was higher in this group.

Primary respiratory problems ranked third (8.8%) among the total number of children admitted toPICU. The clinical range of children with primary respiratorydiseases varied from pneumonia leading to ARDS, Empyema, and pleural effusionespecially in children with malignancies.

Post operative surgical patients formed the next group which constitutes about 8%. About 4 % of total admissions were children with acute gastroenteritis and dehydration; miscellaneous group formed a major proportion (45.6%) which included burns, disseminated tuberculosis, snake bite, poisoning, chronic kidney diseases etc.

Table 4:Clinical diagnoses in our study population

Clinical diagnosis	Frequency	Percentage
CNS diseases	27	21.6%
Sepsis	15	12%
Pneumonia	11	8.8%
Post op laparotomy	10	8%
AGE with severe dehydration	5	4%
Others (Miscellaneous)	57	45.6%

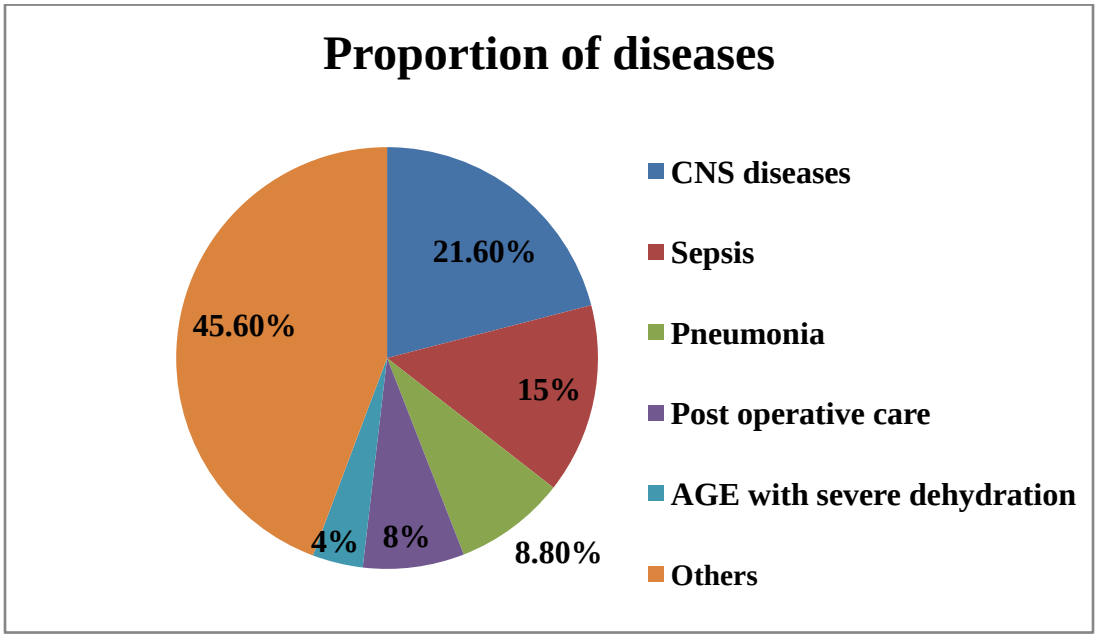


Figure 3: Pie diagram depicting the clinical diagnoses in our study population.

Modalities of Respiratory support:

Among all the one hundred and twenty five children studied, one hundred and twelve children (90%) were on mechanical ventilator support, seven children (5%), required High flow nasal canula therapy, five children (4%) required face mask non invasive ventilator care and one child (0.8%) required nasopharyngeal CPAP (Continuous positive airway pressure) care.

Table 5:Distribution of study population based on respiratory support.

Respiratory support	Frequency	Percentage
High flow nasal canula	7	5.65%
Nasopharyngeal CPAP	1	0.81%
Face mask NIV	5	4.03%
IMV	112	89.52%

X axis - Mode of respiratory support ; Y axis - Percentage

Figure 4: Distribution of study population based on respiratory support

The average Mean Airway Pressure (MAP) was 11.61+/- 6.74mm Hg. The mean airway pressure was obtained from all the ventilated children. The minimum mean airway pressure was 8 and the maximum mean airway pressure was 35 mm Hg.

Oxygenation index was calculated in all ventilated children. The median oxygenation index among all our patients was4.65. The minimum oxygenation index was 0.6 and the maximum was 73.

Similarly, oxygen saturation index was also calculated. The median oxygen saturation index was 5.55. The minimum oxygen saturation index was 1 and the maximum oxygen saturation index was 160. The oxygenation index and the oxygen saturation index were calculated only for the patients who were on mechanical ventilation.

SF ratio was calculated by the oxygen saturation by pulse oximetry /fraction of inspired oxygen (Spo2/Fio2). PF ratio was calculated by the partial pressure of oxygen/fraction of inspired oxygen (Pao2/Fio2).There were 230 data pairs of SF and PF ratios where the mean SF ratio was 180 +/-60.41 and the mean PF ratio was 248+/-156.The mean FiO2 in our study group was found to be 54.21+/-45.25. The minimum FiO2 was 25% and the maximum was 100%.

Table 6: Baseline findings in our study population.

Variables	Mean+/-SD, (Median)	Min-Maximum
Mean airway Pressure	11.61+/-6.74 mmHg	4-68 mmHg
Oxygenation index	7.67, (4.65)	0.6-73
Oxygen saturation index	9.68, (5.55)	1-160
SF ratio	180+/-60.41	25-400
PF ratio	248+/-156	24-808
Fio2	54.21+/-45.25%	25-100%

PIM II score at admission:

The second edition of paediatric index of mortality was used in our children. The mean PIM II score at admission in our study was 27.38.

Table 7: Distribution of patients based on the PIM 2 Score

PIM 2 Score at admission	Percentage
<5	18.5%
5-15	15.38%
15-30	29.2%
>=30	36.9%

18.5% of all children had PIM 2 score less than 5, 15.38% children had PIM 2 score between 5 and 15, 29.2% had PIM 2 score ranging from 15 - 30, while another 36.9% children had PIM2 score more than 30.

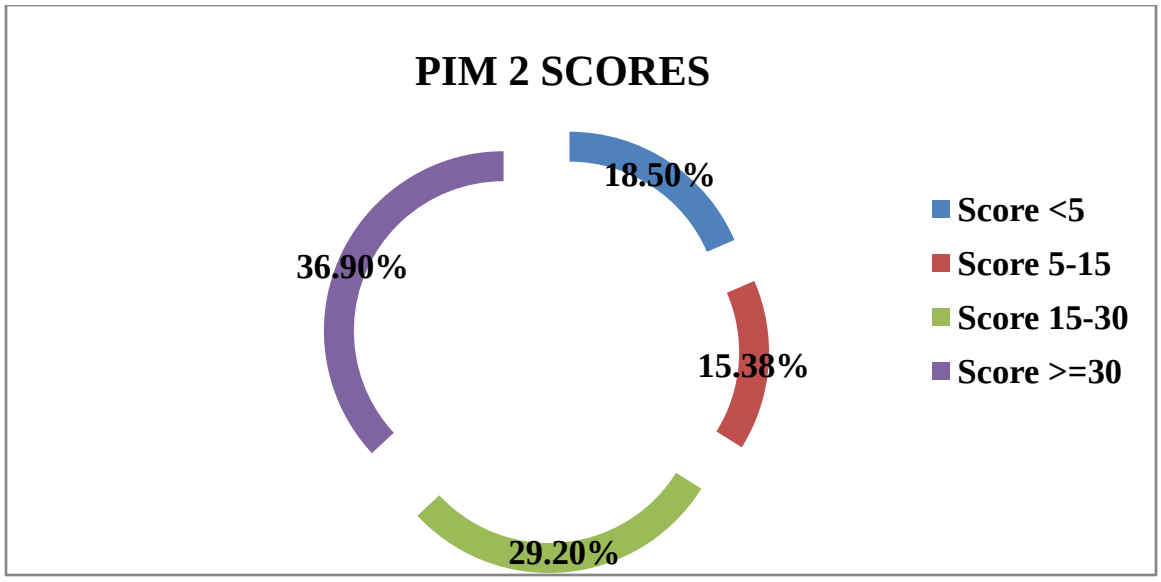


Figure 5: Bar diagram above shows patient distribution based on PIM 2 Score.

Table 8: Mortality rate among our study population based on PIM2 Score.

PIM 2 Score at admission	**Mortality rate**
<5	nil
5-15	40%
15-30	31.58%
>30	41.67%

The maximum mortality was seen in children who had PIM 2 score of >30 followed by 5-15.

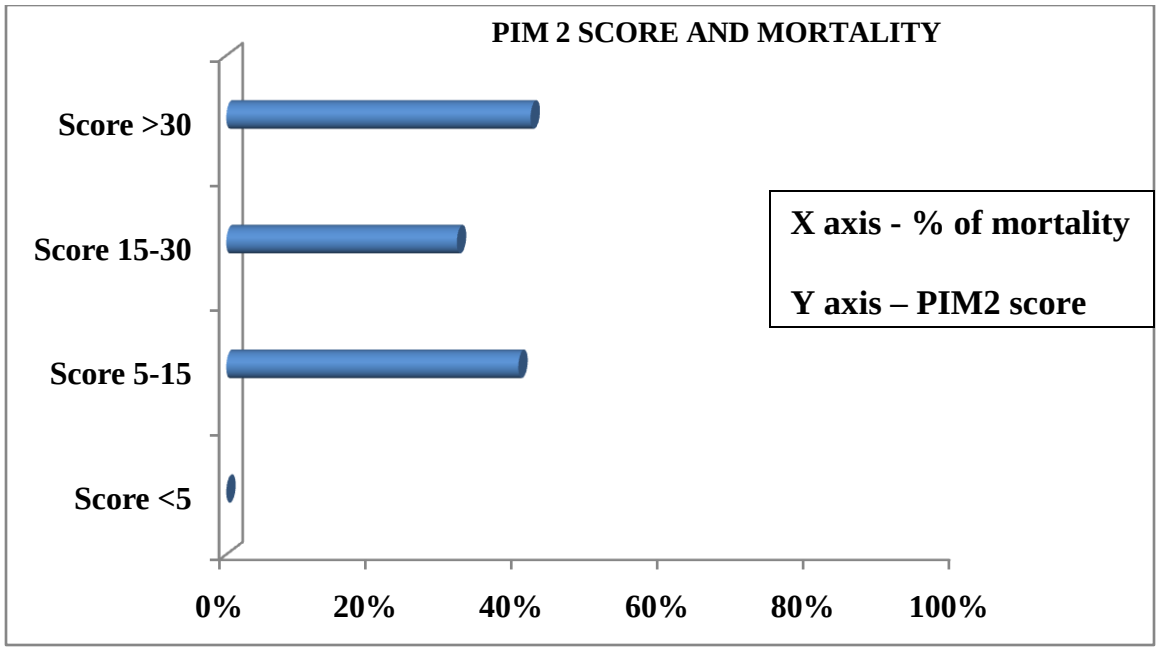


Figure 6: Mortality rate among our study population on the basis of their PIM2 Score

ARDS Vs Non ARDS group:

In our entire study group, a total of 27 patients had ARDS, which constituted about 21.6%, and remaining 99 children (78%) belonged to the Non ARDS group.

Table 9: Children with ARDS.

Group	Frequency	
	Total	Expired
ARDS	27(21.6%)	9(33.3%)
Non ARDS	98(78%)	37(37.7%)

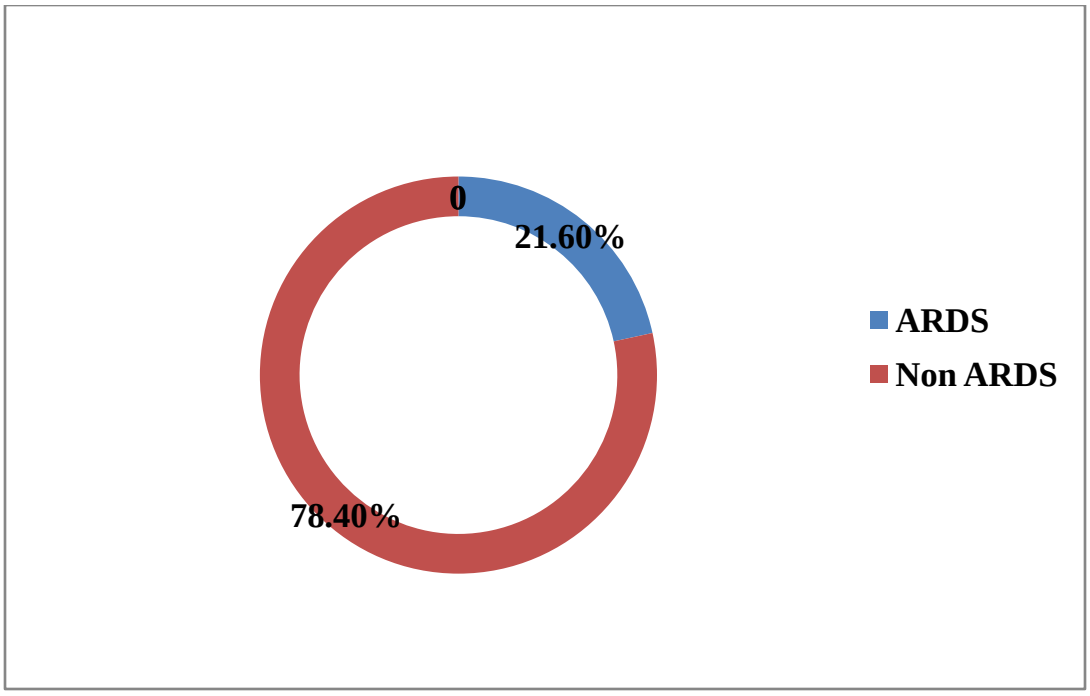


Figure 7: Childrenwith and without ARDS in the study population.

Correlation between SF ratio and PF ratio:

PF ratio and SF ratio was calculated from all children who were on respiratory support with a known oxygen concentration (Fio2). Separate 2 X 2 tables were constructed using PF ratio less than 200 and 300 comparing with SF ratio. The results were summarized in a Receiver Operator Characteristics Curve (ROC). A linear regression equation was derived to explain the relation between SF ratio and PF ratio which is given below.

SF ratio = 134.28 + (0.17 x PF ratio). The p value was less than 0.01 and R^2 was 0.1735.

Table 10: Derivation of linear regression equation and R square

		Std error	t value	95% Conf. Interval
PF ratio	0.1712	0.02818	6.08	0.1154-0.22703
SF ratio	134.28	8.1555	16.47	118.13-150.43

Scatter plot was constructed using the linear regression equation

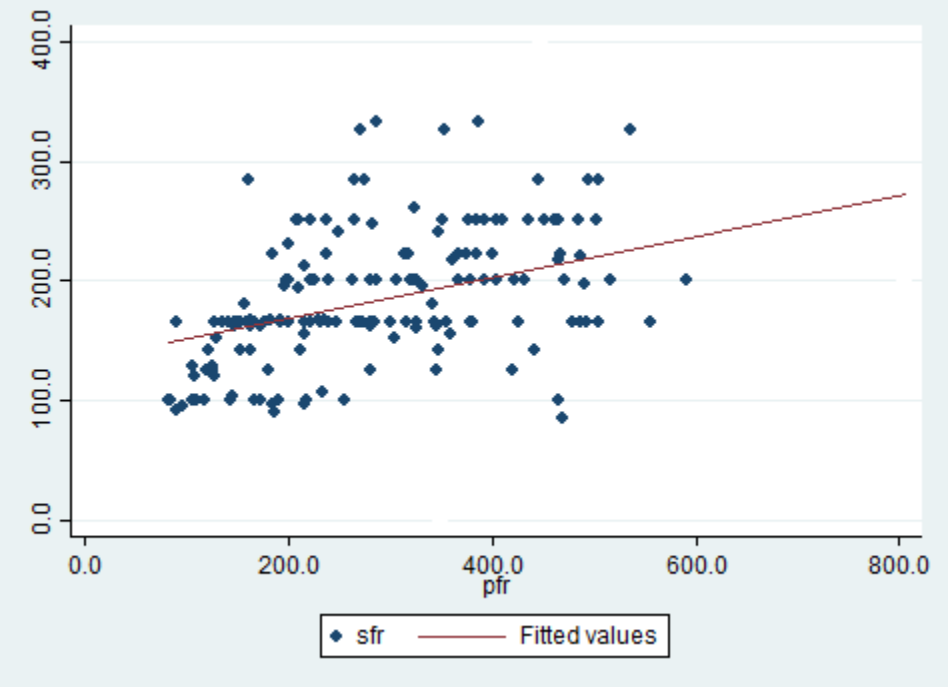


Figure8: Scatter plot with best fit linear regression line for SF ratio and PF ratio

SF ratio = 134.28 + 0.17 (PF) $p < 0.001$, $R^{2} = 0.1735$.

In the **ROC curve for PF ratio less than 200 versus SF ratio**, the area under curve (AUC) was found to be 0.8078 with 95% CI (0.7385 to 0.8771). The ROC curve is depicted below.

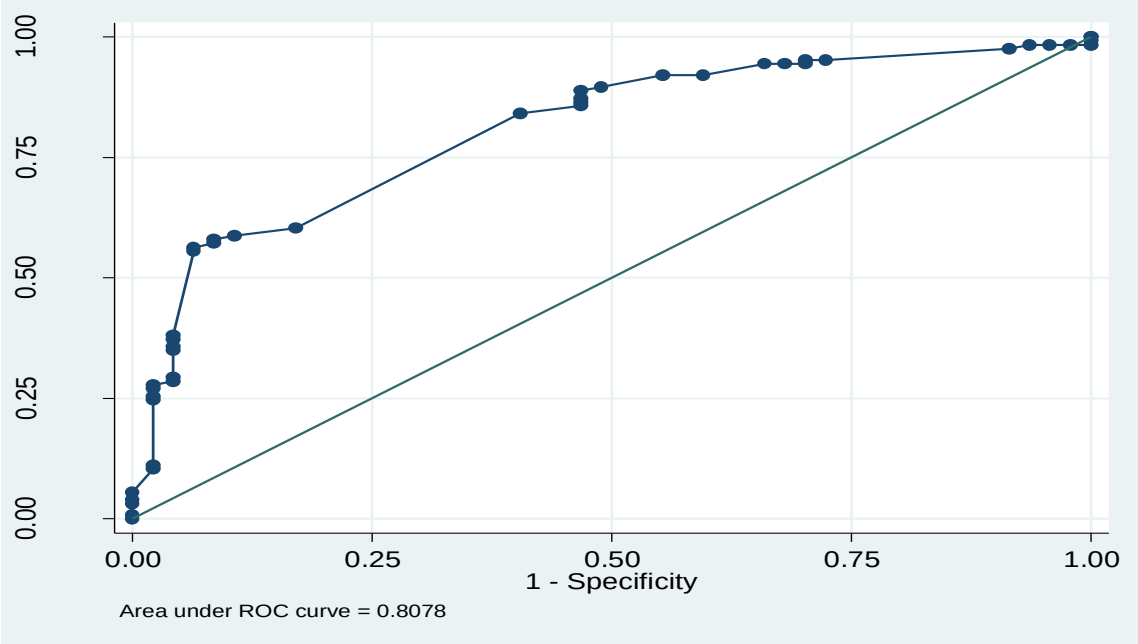


Figure 9: ROC curve showing AUC for PF < 200 Vs SF ratio (0.8078)

The PF ratio < 200 correlated well with SF ratio with area under ROC curve of 0.807. The SF ratio corresponding to PF ratio less than 200 was taken as 180. When SF ratio corresponding to the PF ratio less than 200 was taken as less than 180, the sensitivity was 90% with specificity of 59%, with the positive predictive value of 63.1% and negative predictive value of 84.3%. While the SF ratio cut off was increased to 200, the sensitivity increased to 93%, but the specificity decreased to 56% with the positive predictive value decreased to 62.2% and the negative predictive value increased to 86.6%.

Table 11:Sensitivity/specificity/PPV/NPV for PF <200 Vs SF ratio.

PF Ratio	SF ratio	Sensitivity	Specificity	PPV	NPV	ROC
<200	<166	83%	60%	58.3%	84.8%	**0.8078**
	<180	**90%**	**59%**	**63.1%**	**84.3%**	
	<194	91%	57%	44.8%	94.8%	
	<196	91%	57%	44.3%	94.7%	
	<200	93%	56%	62.2%	86.6%	

In the **ROC curve for PF ratio less than 300 versus SF ra**tio, the area under curve (AUC) was found to be 0.7018 with 95% CI (0.6241to 0.7794). The ROC curve is depicted below.

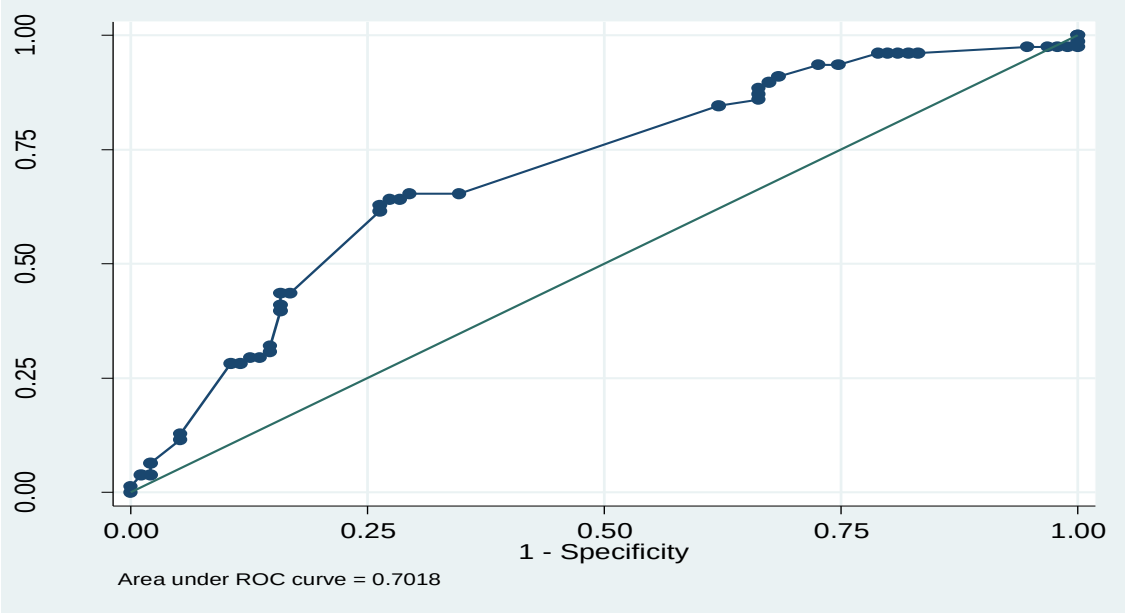


Figure10: **ROC curve showing AUC for PF < 300 Vs SF ratio (0.7018)**

When SF ratio corresponding to the PF ratio less than 300 was taken as less than 180, the sensitivity was 70% with specificity of 65%, with the positive predictive value of 80.9% and negative predictive value of 57.3%. At the same time, when the SF ratio cut off was increased to 200, the sensitivity increased to 73%, but the specificity decreased to 61% and the positive predictive value decreased to 70% and the negative predictive value also decreased to 65.8%.

Table 12: Sensitivity/Specificity/PPV/NPV for PF <300 Vs SF ratio.

PF Ratio	SF ratio	Sensitivity	Specificity	PPV	NPV	ROC
<300	<166	65%	65%	64.2%	68%	**0.7018**
	<180	**70%**	**65%**	**80.9%**	**57.3%**	
	<196	73%	64%	71.1%	65.8%	
	<200	73%	61%	70%	65.8%	
	<213	83%	44%	75%	52.8%	

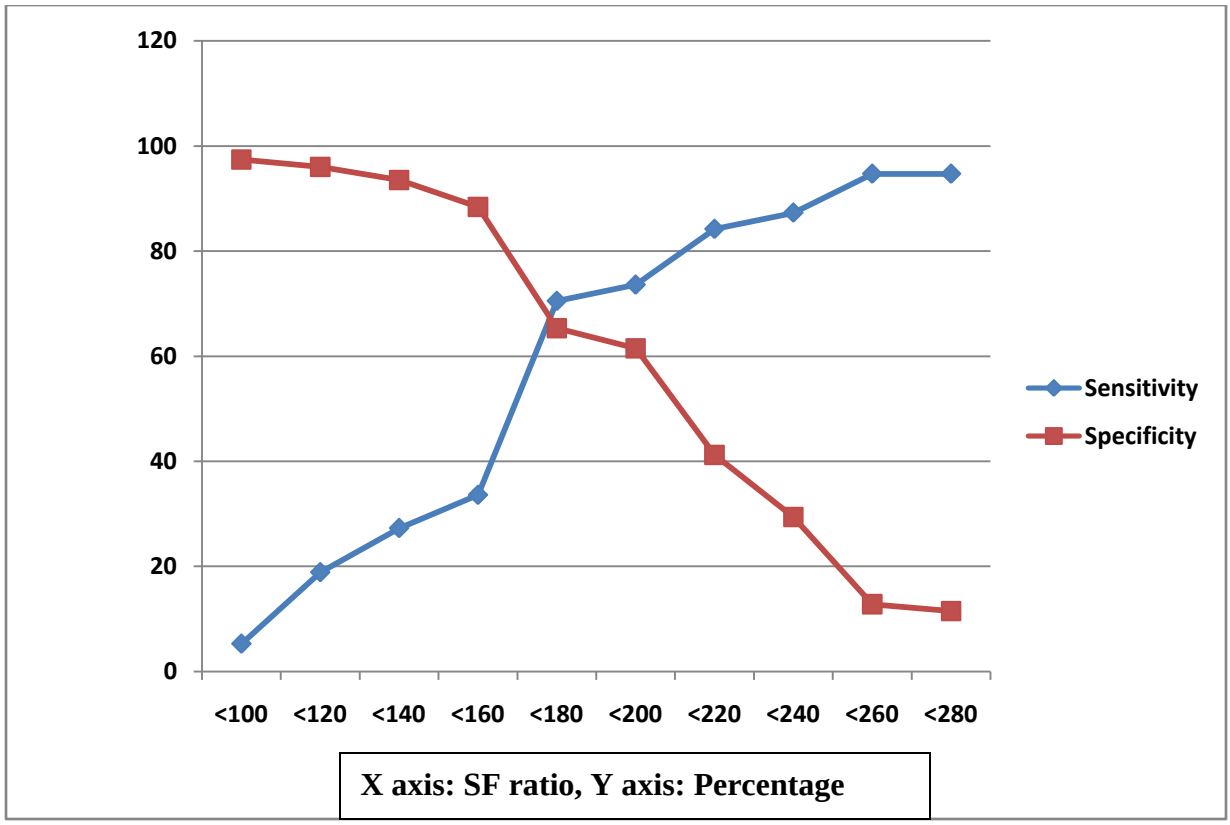


Figure 11: Graph depicting SF ratio with respective sensitivity and specificity

Comparison of Oxygenation index and SF ratio

The recent PARDS guidelines have mentioned that oxygenation index more than four can be considered as ARDS when the child is on invasive mechanical ventilation. Hence, we did look at the correlation between the oxygenation index and SF ratio. The results were summarized in a ROC curve. In the ROC curve for oxygenation index more than four versus SF ratio, the area under curve (AUC) was found to be 0.7048 with 95% CI (0.607 to 0.808). The ROC curve is depicted below.

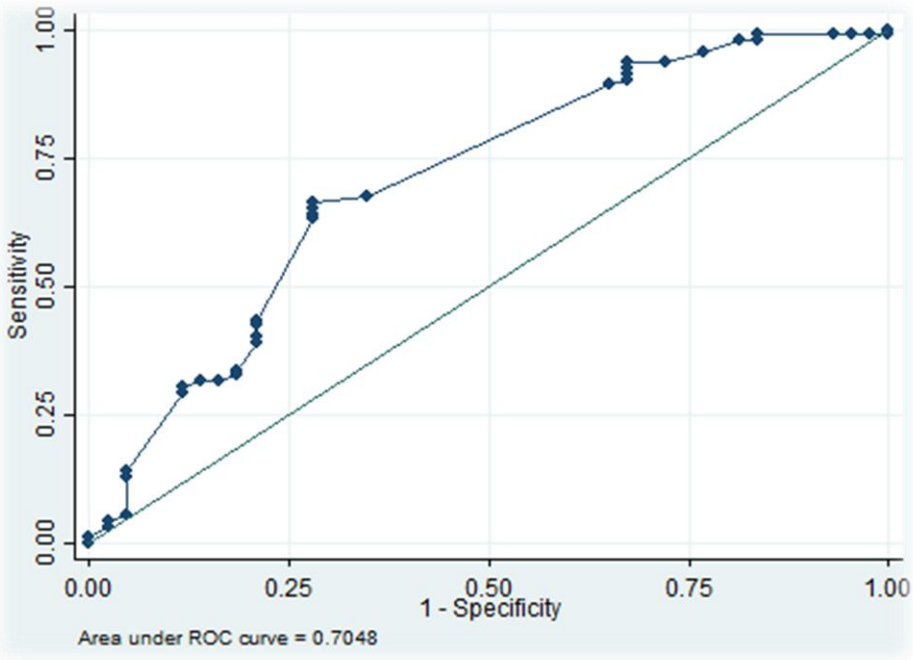


Figure 12: ROC curve showing AUC for OI >4 Vs SF ratio (0.7048)

On comparison of the SF ratios less than 180 and less than 200 with oxygenation index more than 4, SF ratio of less than 180 had a sensitivity and specificity of 72% and 66% respectively and a positive predictive value and negative predictive value of 76% and 74.7% respectively. Hence, it is acceptable that, SF ratio less than 180 can be used to discriminate ARDS.

Table 13: Sensitivity/Specificity, PPV, NPV on comparing OI >4 and SF ratio.

Oxygenation index	SF ratio	Sensitivity	Specificity	PPV	NPV	ROC area
>4	<180	72%	66%	76%	74.7%	0.7048
	<200	84.1%	63.8%	63%	84.5%	

Comparison of Oxygenation Index (OI) and Oxygenation saturation Index (OSI)

Oxygenation saturation index has the advantage of calculating it without the need for a PaO2 which in turn requires an ABG. Hence, obtaining an OSI cut off equivalent to OI more than 4 helps in discriminating children who have ARDS. We analyzed the comparison of oxygenation index (OI) more than 4 and oxygenation saturation index. The results were summarized in a ROC curve (Figure13). In the ROC curve, the area under curve (AUC) was found to be 0.8974 with 95% CI (0.8457 to 0.9491). The ROC curve is depicted below.

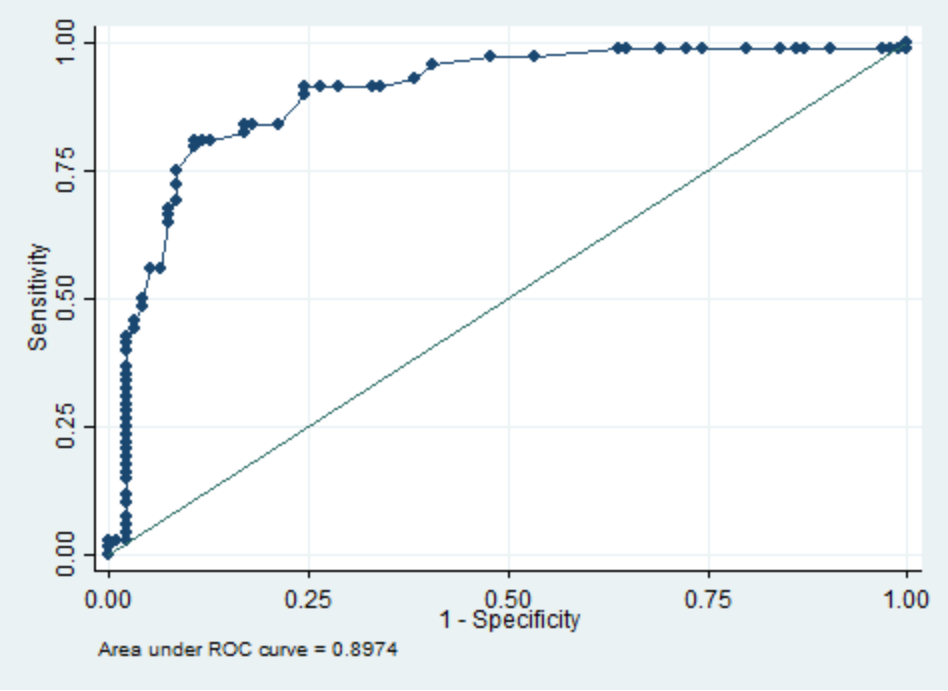


Figure 13: ROC curve comparing Oxygenation index > 4 and oxygenation saturation index

Table 14: Sensitivity/Specificity /PPV/NPV of OI >4 Vs OSI >5.

Oxygenation index	Oxygenation saturation index	Sensitivity	Specificity	PPV	NPV	ROC area
>4	>5	91%	73%	72.9%	92.2%	0.8974

As per the above ROC curve, OSI of more than 5 had 91% sensitivity and 73% specificity and 72.9%, 92.2% positive and negative predictive values respectively to discriminate the children with ARDS.

Hence, in places where arterial blood gas is not available, oxygen saturation index more than 5 can be used to discriminate children with ARDS. This can be reliably applied in children to diagnose ARDS in addition to the SF ratio.

DISCUSSION

Respiratory diseases constitute a significant amount of morbidity and mortality in children. As various studies have mentioned, they are the number one cause for under five deaths globally(1). Hence it is of paramount importance to diagnose and treat these respiratory diseases early.

In the PICU setup, ARDS is one of the important contributors of morbidity and mortality(70). Partial pressure of Oxygenobtained from arterial blood gas is considered to be the gold standard in determining arterial oxygenation status. In critically ill children and young infants obtaining arterial blood gas may be difficult and also increases risk of hospital acquired infection. Moreover, in primary and secondary hospital setting facility for doing arterial blood gas is rarely available. In these setting, SF ratio could be used as a screening tool to assess the severity of respiratory illness and regulates appropriate management and timely referral. Hence, to determine ARDS, SF ratio is being tried as a surrogate marker to PF ratio.

In our study, male children contributed to 66.4% and the remaining 33.6% were female children. The mean age group of our study population was 4 years, 8 months.We hadtwenty seven patients with ARDS at our study cohort showing equal distribution in all the age groups. Likewise, in other intensive care units, mortality in children with ARDS is significant (33%).

The spectrum of diagnoses in our children had a varying range involving all the systems. Children with CNS diseases formed themajority among the admission to our

PICU contrary to the Egyptian study done by Hanna et al looking at the profile of PICU patients which showed Pneumonia as the commonest cause(74). Another large study done at Royal Children's Hospital (RCH), Melbourne looking at the profile of children found congenital cardiac disease as the commonest cause for the PICU admission followed by respiratory disease(75). This variation could be attributed to multiple factors including the geographical distribution, prevalence of epidemics and available healthcare system.

Paediatric Index of Mortality was originally developed by RCH for the prognostication of children getting admitted to pediatric intensive care units. PIM 2 score was introduced in 2003, which was used in our study(75). The maximum number of mortality (33; 42%) was seen in children who had higher PIM 2 score, which is more than thirty in our study. The mean PIM 2 score at our study group was 27.38. However the same was not statistically significant as the p value was just above the acceptable range (p value - 0.06). The probable reason for the statistical insignificance in our study population may be due to the increased number (32; 40%) of deaths in the children belonging to PIM 2 score of 5 to 15. This increase in number of deaths among children with lower score range may be further explained by hospital acquired infection.

In our study, we have shown that, SF ratio of less than 180 corresponds well with PF ratio criteria used for ARDS. This value of 180 is derived from the linear regression equation. With the SF ratio value being less than 180, the sensitivity and specificity to

discriminate ARDS in children is 70% and 65% respectively. The positive predictive value and the negative predictive was 80.9% and 57.3%.

Thomas et al in their study among children where they found an SF ratio cutoff value of 212, which could predict the ARDS in children with a sensitivity of 76% and specificity of 83%(76). The same study also found that SF ratio cutoff less than 253 could predict acute lung injury with 93% sensitivity and 43% specificity.

Bilan et al did a similar study comparing the PF ratio and SF ratio in children, which also found a good correlation between both the ratios. This study identified SF ratio cut off 181 and 235 to diagnose ARDS and Acute lung injury respectively. The SF ratio cut off described had 71% sensitivity and 82% specificity to diagnose ARDS. There was 100% specificity and 57% sensitivity to diagnose Acute lung injury(12).

A prospective study done by Rice et al, in adults identified higher values of SF ratios to correlate with the PF ratio criteria used for ALI and ARDS(13). They found a cutoff less than 235 and 315 for ARDS and ALI respectively, with 85% sensitivity and 85% specificity for ARDS with AUC of 0.929 and 91% sensitivity and 56% specificity for diagnosing ALI with AUC of 0.920. Practically, this means patients saturating 95% with Fio2 of 30% will be considered as acute lung injury and those saturating 94% with 40% Fio2 will be considered as ARDS.

The recent PARDS guidelines also had kept a higher cut off of 264 to diagnose ARDS in places where arterial blood gas is not available(44). In practical situations, a child who is on a respiratory support with FiO2 of 36% when saturating 94% will be considered as ARDS.

. As per our study cut off value for SF ratio of 180, children will fall in the category of ARDS only when they require FiO2 of 50% with 90% saturation or at a saturation of 94%, when the FiO2 requirement goes up beyond 52%.

We did look at other cut off values for SF ratio considering the sensitivity, specificity and relevancy of clinical situation. For example, if you consider the SF ratio cut off at<220, any saturation of 88% or less with Fio2 of 40% or more will be characterized as ARDS. For the same child we increase the Fio2 to 45% and if the Spo2 improves to 99%, still we classify the patient to have ARDS as the SF ratiobeing less than 220. But at bed side,practically we tend to titrate the Fio2, till the Spo2 improves more than 90 to 94%. In that case, we may be increasing Fio2 from 40 to 50% gradually. If at thisFio2 of 50% (i.e., Face mask oxygen 8 to 10 lit/min), the patient saturates only 90% or less (i.e., SF ratio<180), then the patient is more likely to have ARDS. Hence, we consider that SF ratio with a cut off <180 is more relevant and practical to diagnose Paediatric ARDS in our clinical setting.

As per PALICC group consensus recommendation, children who receive fio2 of ≥ 40% (i.e. if they are on a low flow o2 device <1 year ; 2 l/min., 1 – 5 years old : 4 l/m,

5 – 10 years : 6 l/m, >10 years : 8 l/m of oxygen) to attain a Spo2 between 88 to 97% (SF ratio 220 to 242) is categorized as at risk of developing Paediatric ARDS(44).

Although we made an attempt to correlate PF ratio less than 200 with SF ratio,which found to be correlating well with 90% sensitivity and 59% specificity along with good AUC of 0.8, the recent PARDS guidelines have not mentioned anything in particular to PF ratio less than 200. The term acute lung injury is not being used anymore and the current PALICC guidelines clearly mention PARDS as PF ratio less than 300 (non-invasive ventilation) or Oxygenation index more than 4 for children with invasive ventilation.

In our study, we also compared SF ratio and oxygenation index more than four and found a good correlation with an AUC of 0.739.The recent PARDS guidelines have givenOxygen saturation Index (OSI) cut off more than 5 to diagnose ARDS. When we compared oxygenation index more than 4 with oxygen saturation index, we found a good AUC of 0.897 in the ROC with 91% sensitivity and 73% specificity to diagnose ARDS. Thus, we validated this guideline in our study.

In general, previous studies done to correlate SF and PF ratio shows varying cut off values for SF ratio in each study. But, there exists a strong correlation between the two ratios's, which is the common baseline message available from all the studies. As per the objectives of our study, we have brought out an SF ratio cut off of 180 for ourchildren to diagnose ARDS clinically in our context. This can be applied to the places where

arterial blood gases are not available and this can also be used in PICU to monitor the course and progress of ARDS.

The usage of SF ratio instead of PF ratio has added following benefits in our clinical setting(69):

- S/F ratio using Pulse oximetric measurement of saturation, helps in easier assessment of oxygenation status and helps in early identification of children at risk of ARDS

- Placement of arterial lines in critically ill children and young infants is difficult and they are not used routinely. Hence, having a non invasive tool (SF) as a surrogate marker for PF ratio will help for screening purposes

- In ICU settings, PF ratios are used in calculating few scores like Paediatric risk of mortality score, Paediatric index of mortality 2, Paediatric logistic Organ dysfunction (PELOD score) thereby helps in risk assessment and characterization of the disease. In situations where, ABG is not done and PF ratios are not available, a normal value is substituted. Hence in these conditions, SF ratio can be used to get a proper overall risk assessment instead of using the scores without proper arterial blood gas values

- Association between SF and PF ratio is stronger in paediatric population. However, it is said that arterial oxygen saturation (Sao2) marks the severity of pulmonary disease than PF ratio. So, based on this, Spo2 being an accepted substitute for arterial oxygen saturation, SF ratio is used reliably than PF ratio in appropriate clinical settings.

- SF ratio can be reliably used in secondary level settings as a noninvasive screening tool to assess the severity of respiratory illness where ABGfacility is not available.

SUMMARY

- This study was done in Pediatric Intensive Care Unit of Christian Medical College, Vellore for a time period of seven months. Our study had total of one hundred and twenty five children of which twenty seven had ARDS. Two arterial blood gases from each patient were taken for our study with corresponding PaO2 and SpO2. Thus, we had 230 data pairs of SF and PF ratio

- According to our study, we found that there is astrong correlation between SF ratio and PF ratio. The relation between SF ratio and PF ratio was explained by constructing a Scatter plot, using the following linear regression equation
    - SF ratio = 134.28 + 0.17 (PF) $p < 0.001$, $R^{2} = 0.1735$

- SF ratio less than 180 correlates well with PF ratio less than 300 to diagnose ARDS in children. The sensitivity and specificity to diagnose ARDS was 70% and 65% respectively, with the positive predictive value of 80.9% and negative predictive value of 57.3%. The Area under curve for ROC comparing PF <300 with SF ratio was 0.701 with 95% CI (0.6241to 0.7794)

- The PF ratio < 200 correlated well with SF ratio with area under ROC curve of 0.807. The SF ratio corresponding to PF ratio less than 200 was taken as 180 where the sensitivity was 90% with specificity of 59%, with the positive predictive value of 63.1% and negative predictive value of 84.3%.

- In the comparison between oxygenation index > 4 with SF ratio, good correlation was observed with area under curve (AUC) of 0.7048 with 95% CI (0.607 to 0.808). SF ratio of less than 180 had a preferable sensitivity and specificity of 72% and 66% respectively and a positive predictive value and negative predictive value of 76% and 74.7% respectively.

- Oxygen saturation index more than 5 was found to discriminate children with ARDS when compared with oxygenation index, the area under curve (AUC) of which was found to be 0.8974 with 95% CI (0.8457 to 0.9491). This also had 91% sensitivity and 73% specificity along with positive predictive value of 72.9% and 92.2% negative predictive value.

CONCLUSIONS
&
LIMITATIONS

Our study shows that SF ratio can be used as a reliable, non-invasive, surrogate marker for PF ratio to diagnose ARDS and also as a screening tool to assess the severity of respiratory illness in resource limited settings where arterial blood gas is not available

Limitations:

1. Number of children with ARDS is less in our study group.
2. Another limitation with this study is the requirement of known FiO2 as one of the variable, which may not be available in all settings. In places where an arterial blood gas is not available, SF ratio can be used, however the FiO2 should be known. Having a set of pre formed FiO2 values like in the chart given below can help at those settings(33).

Oxygen device	**Oxygen administered**	**FiO2 delivered**
Nasal prongs	1 Litre /min	24%
	2 Litre/min	27%
	3 Litre/min	30%
	4 Litre/min	33%
Simple mask	6 -10 Litre/min	35-50%
Non –rebreathing mask	12-15 Litre/min	80-100%
Venturi mask	4 Litre/min	24-28%
	6 Litre/min	31%
	8 Litre/min	35-40%

3. We have derived a SF cutoff of 180 as a surrogate marker for PF ratio <300 to differentiate children with ARDS. This SF ratio value needs further validation studies which will be continued in our PICU

4. Fio2 of some of the PICU patients haven't been titrated to achieve Spo2 of 97% (from 100%) as per PARDS guidelines.

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ANNEXURES

STUDY PROFORMA

"Comparison of PaO2 /FiO2 (PF) RATIO AND SpO2/FiO2 (SF) RATIO in critically ill children requiring respiratory support in a tertiary care center in South India"

1. Name : 2. Sex : 3. Age :

4. Hospital No : 5. Time of admission :

6. Date of admission: 7. Diagnosis on admission:

8. Pre existing morbidity if any :

9. Oxygen support : a) Airvo b) CPAP c) NIV d) IMV

10. PIM II SCORE AT ADMISSION:

VARIABLE	VALUE	PATIENT
a. Systolic BP(mmHg)	- Measured value - If unknown =120 - Cardiac arrest= 0 - Shock with unmeasured SBP = 30	
b. Pupillary reaction to light	->3mm & both fixed =1 - Other/unknown =0	
c. FiO2 X100/ PaO2(mmHg)	- Measured value - If unknown = 0	
d. Base excess (mmol/l)	- Measured value - If unknown = 0	
e. Mechanical ventilation at any time during the 1st hr in PICU	-Yes = 1 -No = 0	
f. Elective admission To PICU	-Yes = 1 -No = 0	
g. Recovery from surgery/procedure is the main reason for admission	-Yes = 1 -No = 0	
h. Admitted following cardiac bypass	-Yes = 1 -No = 0	
i. High risk diagnosis is the main reason for admission: - Cardiac arrest,SCID - Leukemia/lymohoma after 1st induction - Spontaneous cerebral hemorrhage - Cardiomyopathy/myocarditis - HIV infection,Liver failure - Neurodegenerative disorder	-Yes = 1 -No = 0	
j. Low risk diagnosis is the main reason for admission:	-Yes = 1 -No = 0	

- Asthma,Bronchiolitis,Croup - Obstructive sleep apnoea,DKA		

S.No	Vital Parameters	At Admission	At 24 hours/worsening
1	Heart rate		
2	Respiratory rate		
3	Saturation		
4	Fio2		
5	MAP		
6	PaO2		
7	Oxygenation index		
8	Oxygen saturation index		
9	S/F ratio		
10	P/F RATIO		

ARDS CRITERIA:

S. No		Yes/No
1.	Age (Exclude patients with perinatal related lung disease)	
2.	Timing (Within 7 days of known clinical insult)	
3.	Origin of Edema (Respiratory failure not fully explained by cardiac failure or fluid overload)	
4.	Chest finding (findings of new infiltrates consistent with acute pulmonary parenchymal disease)	
5.	Oxygenation : I) INVASIVE MECHANICAL VENTILATION : a. Mild : < 4 OI < 8, 5 < OSI < 7.5 b. Mod : < 8 OI < 16, 7.5 < OSI < 12.3 c. Severe : OI > 16, OSI > 12.3 II) NON INVASIVE MECHANICAL VENTILATION : a. Full facemask bi level ventilation or CPAP > 5 cm b. PF ratio < 300 or SF ratio < 264	

OUTCOME	DISCHARGED	DIED	DAMA

Data sheet:

slno	age	sex	toa	doa	diag	morbidi	oxygen	pimscore	hra
1	0.01	2	21.1	13/02/2016	INTRAVENTRICULAR HEMORRHAGE	NIL	4	39.5	124
2	0.11	1	13.3	15/01/2016	SEIZURE DISORDER	DEVELOPMENTAL DELAY	4	9	178
3	12	1	18	16/02/2016	SHOCK	AV CANAL DEFECT, SEVERE MR	3	7.6	110
4	0.01	1	14.3	17/02/2016	SEPSIS	NIL	4	82.5	138
5	5	2	16.4	17/02/2016	JORRP	NIL	4	0.2	104
6	13	2	15.3	18/07/2016	STATUS EPILEPTICUS	NIL	4	29.7	122
7	0.07	2	19.55	19/02/2016	ARDS WITH PNEUMONIA AND SHOCK	NIL	4	25.5	170
8	0.09	2	12.2	21/02/2016	STATUS EPILEPTICUS	NIL	4	62.6	164
9	0.1	2	3.3	23/02/2016	AGE+SEVERE DEHYDRATION, ARDS	NIL	4	53.9	180
10	14	2	10	24/02/2016	PROBABLE MENINGOENCEPHALITIS	NIL	4	36.1	78
11	14	1	9.3	09/03/2016	SNAKE BITE	NIL	4	51	122
12	9	1	12.4	29/02/2016	VENOUS MALFORMATION LEFT SIDE OF NECK	HYPOSPADIASIS	4	0.1	62
13	2	1	10.55	05/03/2016	CHRONIC KIDNEY DISEASE	CKD	4	68.9	133
14	4	1	4.15	29/02/2016	STATUS EPILEPTICUS		4	61.3	160
15	0.03	2	13.5	28/02/2016	ASPIRATION PNEUMONIA	NIL	4	41.5	140
16	6.06	2	20	06/03/2016	APPENDICULAR PERFORATION	NIL	4	3.3	185
17	1.06	1	8.25	10/03/2016	BRONCHOPNEUMONIA	NIL	4	0.2	181
18	1	2	11.3	13/04/2016	GUILLIAN BARRE SYNDROME	NIL	4	2.3	170
19	2	1	14.3	12/03/2016	PARIETO OCCIPITAL EPENDYMOMA	NIL	4	20.7	158
20	0.04	1	10.45	13/06/2015	DENGUE SHOCK SYNDROME, ARDS	NIL	4	38	144
21	4	1	23.55	15/03/2016	STATUS EPILEPTICUS	GLOBAL DEVELOPMENTAL DELAY	4	58.5	139
22	0.01	1	23	16/03/2016	PUV FULGRATION POST OP	NIL	4	2	124
23	6	1	23.3	29/03/2016	PRADOR WILLI SYNDROME	NIL	1	15.2	135
24	0.09	1	13.3	20/03/2016	SEPTIC SHOCK	NIL	4	11.3	161
25	5	1	2.15	20/03/2016	ACUTE MENINGOENCEPHALITIS	TYPE 1 DIABETES	4	22.2	158
26	10	1	18.3	23/03/2016	DENGUE SHOCK SYNDROME	NIL	4	49	159
27	11	1	17.3	23/03/2016	DEVELOPMENTAL DELAY	GDD	4	13.6	75
28	8	1	1	23/03/2016	ACUTE MENINGOENCEPHALITIS	NIL	4	9.9	125
29	2.06	2	13.2	26/03/2016	ACUTE ENCEPHALOPATHY	NIL	4	16.1	144
30	10	1	2.15	25/03/2016	T CELL ALL - MEDIASTENAL MASS	T CELL ALL	1	48.7	135
31	1	1	20	27/03/2016	STATUS EPILEPTICUS	SEIZURE DISORDER	4	22.6	135
32	0.09	1	23	29/03/2016	MAXILLO MANDIBULAR TUMOR EXCISION	NIL	4	0.4	130
33	11	1	13.3	29/03/2016	STEVEN JOHNSON SYNDROME - SEPTIC SHOCK	NIL	4	31.2	140
34	8	1	19.5	29/03/2016	T CELL ALL	NIL	4	88.2	160
35	2	2	22.1	29/03/2016	POST OP LAPAROTOMY	NIL	4	4.5	150
36	3	1	15	04/04/2016	SUSPECTED GBS	LOWER RESPIRATORY TRACT INFECTION	4	1.1	135
37	2	1	13.3	05/04/2016	EVISCERATION COLON	NIL	4	0.2	160
38	15	1	16	06/04/2016	BLUNT INJURY ABDOMEN	NIL	4	0.5	125
39	3	1	15.45	09/04/2016	MITOCHONDRIAL CYTOPATHY		4	25.5	110
40	15	2	19.2	08/04/2016	MENINGOENCEPHALITIS	NIL	4	20.8	145
41	14	1	23	13/04/2016	PARTIAL HANGING	NIL	4	37.9	152
42	12	1	2	13/04/2016	MENINGITIS WITH HYDROCEPHALUS	HEPATITIS A	4		159
43	6	2	1.1	15/04/2016	SEIZURE DISORDER	NIL	4		182
44	14	1	1	17/04/2016	T CELL ALL	NIL	4		135
45	5	1		16/04/2016	SEIZURE DISORDER	NIL	4		110
46	0.06	2	15.3	17/04/2016	CONGENITAL EVENTERATION OF DIAPHRAGM	NIL	4		125
47	0.05	2	19.3	25/04/2016	FEBRILE SEIZURES	NIL	4	38.2	160
48	3	1	21	25/04/2016	SEPTIC SHOCK, OP POISONING	NIL	4		165
49	15	1	19.5	26/04/2016	RTA, HAEMOPNEUMOTHORAX, HAEMOPERITONEUM	NIL	1	26.6	130
50	5	1	17	27/04/2016	HEPATIC ENCEPHALOPATHY	NIL	4		130
51	7	2	20	28/04/2016	ENCEPHALITIS	NIL	4	19.3	153
52	0.07	1	8	29/04/2016	STATUS EPILEPTICUS - CRYPTOGENIC EPILEPSY	NIL	4		134
53	4	1	17.3	01/05/2016	GBS - ACUTE FLACCID PARALYSIS		4	18.8	128
54	9	2	19.1	02/05/2010	RTA		4		104
55	13	2	22.3	02/05/2016	UNKNOWN BITE		4	19.5	135
56	3.04	1	23.05	03/05/2016	SEVERE PNEUMONIA		1		114
57	5	2	4.1	05/05/2016	SUPER REFRACTORY STATUS EPILEPTICUS - MODS		4		139
58	1	2	14.3	06/05/2016	RIGHT UPPER LOBE COLLAPSE	NIL	4		142
59	10	1	20.25	05/05/2016	DIABETIC KETOACIDOSIS		1		134
60	3	1	9	07/06/2016	GBS		4		147
61	1.05	1	18.4	11/05/2016	ENTEROCOCCUS MENINGOENCEPHALITIS		4	37.6	123
62	1	1	19	12/05/2016	GLYCOGEN STORAGE DISEASE TYPE I		4	22.2	145

hr24	rra	rr24	sata	sat24	fio2a	fi0224	mapa	map24	pa02a	pa0224	oia	oi24	osia	osi24	sfra	sfr24	pfra	pfr24	ards	outcome
137	44	45	98	100	100	45	12	50	216	142	5.5	15.8	12.2	22.5	98	222	216	315	2	1
135	20	25	100	100	100	50	8	10		202		2.5		5	100	200		404	2	3
110	38	27	100	100	60	40	17	10		106		3.7		4		250		265	2	1
105	30	25	97	100	65	50	31	12		161		3.7		6		200		322	2	1
125	20	20	100	100	60	60	17	15	84		12.1		10.2		166		140		2	1
96	20	20	100	100	80	50	8	9	277	216	2.3	2.1	6.4	4.5	125	200	346	432	2	1
165	50	25	100	100	70	50	15	8		113		3.5		4		200		226	1	1
161	25	25	100	100	60	40	9	11	470	151	1.1	2.9	5.4	4.4	166	250	783	377	2	1
170	30	31	98	100	60	50	10	8		196		2		4		200		392	1	3
98	15	12	100	100	60	35	11	9		215		1.4		3.1		285		160	2	2
150	16	20	100	98	60	25	4	7	296	112	0.8	1.5	2.4	1.7	166	400	493	448	2	1
115	15	17	88	98	60	60	7	9		98		5.5		5.4		166.6		163.3	2	1
137	20	21	96	92	100	40	7	16	95	80	7.4	8	7	7	96	230	95	200	2	1
131	21	15	100	100	60	40	9	6		201		1.2		2.4		250		502.5	2	1
	30		98		90		16		79		18.2		14.2		108		182		2	3
162	25	21	97	99	75	38	21	12	94	123	16.8	3.7	16.2	4.6	129	260	125	323	2	1
151	39	25	88	100	70	60	23	13		95		8.2		7.8		166		158	2	1
	20		100	96	70	60				89						166		148	2	1
142	25	20	100	100	60	45	7	7	333	211	1.3	1.4	4.2	8.1	166	222	555	466.8	2	1
121	30	30	98	99	100	60	19	14	117	142	16.2	5.9	19	8.4	100	166.6	117	236	1	1
123	20	20	100	100	100	45	19	10		169		2.7		4.5		222		375	2	1
125	31	30	100	100	100	40	13	6		164		1.5		2.4		250		410	2	1
	54		100		60														2	2
160	25	25	100	100	60	60	16	14	256	129	3.8	6.5	9.6	8.4	166	166	426.6	215		1
99	25	25	100	100	100	60	18	6		292				3.6		166		486.6	2	2
170	20	17	98	98	100	60	20	16	465	104	4.3	9.2	20.4	9.7	100	163	465	173.3	2	2
118	20	17	100	100	60	40	10	6		83		2.9		2.4		250		207.5	2	1
148	20	20	100	100	60	50	8	8		99		4		4		200		198	2	1
133	26	25	100	100	60	50	8	8		163		2.4		4		200		326	2	3
120	35	30	100	100	60	50			81	183					166	200	135	366	2	1
132	18	25	100	100	50	45	8	7	236	165	1.6	1.9	4	3.1	200	222	472	366	2	1
128	20	20	100	100	65	60	8	7		109		3.8		4.2		166.6		181.6	2	1
145	20	20	99	99	60	60	22	11	115		11.4		13.3		166.6		191.6		2	2
156	20	29	96	90	60	70	12	13		79		10.1		128		128		112	2	1
140	22	23	100	100	46	46	9	9	363	214	1	1.7	4.1	4.1	217	217	362	466	2	1
130	20	20	100	100	65	45	10	9	84	83	7.7	4.8	6.5	4	153	222.2	129.2	184.4	2	1
168	20	28	100	98	50	30	10	9		81		3.3		2.7		326.6		270	2	1
122	20	18	100	100	60	29	7	24	228	116	1.8	6.2	4.2	7.2	166	333	380	386	2	1
132	20	20	100	100	60	50	8	16	133	140	2.4	5.7	4.8	8	166	200	221	280	2	1
146	16	12	100	100	50	40	11	11	211	95	2.6	4.6	5.5	4.4	200	250	422	237	2	2
148	15	15	100	100	60	60	8	11		138		4.7		6.6		166.6		230	2	2
136	17	15	100	100	45	40	7	7	143		2.2		3.1		222.2		317		2	3
103	20	25	100	100	100	30	9	8		86		2.7		2.4		333		286	2	1
112	15	15	100	100	70	45	18	12	107	107	11.7	5	12.6	5.4	142	222	152	237	2	1
126	18	18	100	100	100	60	21	22	254	144	8.2	9.1	21	13.2	100	166	254	240	2	1
139	30	25	100	100	60	60	12	12		92		7.8		7.2		166		153	2	1
163	33	33	98	98	100	60	24	8	185	207	12.9	2.3	24.4	4.8	98	163	185	345	2	1
132	20	20	100	100	60	45	12	10		173		2.6		45		222.1		384	2	3
100	40	35	100	100	80	50			225	160					125	200	281	320	2	1
137	20	20	100	100	30	35	7	7		93		2.6		2.5		285		265	2	2
145	20	20	100	100	60	45	9	8	132	141	4.1	2.5	5.4	3.6	166	222	222	313	2	1
136	25	25	100	100	40	50	8	8		222		1.8		4		200		222	2	1
145	35	45	100	100	40	30	11	9	88		5		4.4		250		222		2	1
110	20	16	100	100	40	40	10	8	185	186	2.1	1.7	4	3.2	250	250	462	465	2	1
106	18	18	100	100	100	30	22	17	167	106	13.1	4.8	22	5.2	100	326	167	353	2	1
152	43	50	97	94	70	60				130						156		216	1	2
150	30	25	96	99	60	50		21		105		10		10.8		194		210	2	2
122	24	20	94	100	80	70	21	12		149		5.6		8.4		142		212	2	1
119	43	41	99	100		80			367	96						125		120	2	1
141	23	25	75	99	40	40	10	10		113		3.6		4.1		247		282	2	1
100	30	24	100	100	60	60	11	10	272	128	2.4	4.6	6.6	6	166	166	272	128	2	3
152	30	30	100	100	60	60	14	13	180		4.6		8.4		166		300		2	3

63	4	1	20	15/04/2016	MITOCHONDRIAL ENCEPHALOPATHY, STATUS EPILEPTICUS	NIL	4		123
64	5	1	17	03/05/2016	PERICARDIAL EFFUSION	NIL	4	5.5	121
65	12	1	21	14/05/2016	BURNS	nil	4		153
66	0.01	2	19.3	16/05/2016	SEPSIS WITH ASD, PDA		4	14.7	
67	12	1	18.3	19/05/2016	SEPSIS		1		90
68	2	1	9	22/05/2016	POST BMT WITH MEASLES PNEUMONIA	SCID	1	70.6	138
69	0.01	1	9.3	01/06/2016	INBORN ERROR OF METABOLISM		4		146
70	1.06	1	17.4	02/06/2016	SEPTIC SHOCK WITH ARDS		4		150
71	15	1	5	26/05/2016	STATUS EPILEPTICUS			4	150
72	1	1	2	05/06/2016	FOREIGN BODY ASPIRATION		4		140
73	2	2	8	03/06/2016	AGE WITH SEIZURE DISORDER		2		134
74	14	1	2.3	07/06/2016	DISSEMINATED TUBERCULOSIS		4		125
75	0.08	2	11.45	10/06/2016	INTRACRANIAL BLEED		4		168
76	0.01	1	22	13/06/2016	SEIZURE DISORDER		4		140
77	0.01	1	23.55	15/06/2016	POST OP HERNIA PREPAIR`		4	30.6	127
78	9	2	17.3	15/06/2016	SUBGLOTTIC MASS - POST OP DEBRIDEMENT		4		87
79	4	2	8	15/06/2016	ALL		3	24.6	150
80	0.04	1	17	16/06/2016	BARTERS SYNDROME	CYSTIC FIBROSIS	4		115
81	1	2	19	21/06/2016	CHOLEDOCHAL CYST	NIL	4	14.6	110
82	4	2	13	22/06/2016	HYPOTENSIVE SHOCK WITH IC BLEED	GLIOBLASTOMA GRADE IV	4		120
83	5	1	15	22/06/2016	SNAKE BITE		4	26.1	135
84	7	1	21	22/06/2016	HYDATID CYST		4	11	146
85	11	1	1.3	25/06/2016	RTA		4		120
86	0.03	1	12.45	28/06/2016	SEIZURE DISORDER		4	33.4	161
87	0.05	2	11	27/06/2016	ASD WITH PDA	NIL	4		157
88	14	2	0	28/06/2016	SEPTIC SHOCK		3		135
89	13	1	10	30/06/2016	SNAKE BITE		4	34.1	163
90	1	1	22.3	04/07/2016	AML - INTESTINAL OBSTRUCTION		4	29.6	131
91	0.01	1	1	03/07/2016	CONGENITAL DIAPHRAGMATIC HERNIA		4	12.1	152
92	1	1		04/06/2016	ACUTE EPIGLOTITIS		4	25.3	108
93	8	2	19.45	07/07/2016	PROBABLE DIPHTERIA		4		130
94	6	2	17	13/07/2016	CHRONIC LIVER DISEASE		4		120
95	0.02	1	8	13/07/2016	SEPSIS, CLEFT LIP		4		107
96	0.03	1	17.05	14/07/2016	SPINAL MUSCULAR ATROPHY		4		121
97	1	1	15	14/07/2016	HYDROCEPHALUS WITH PIERRE ROBIN SEQUELAE	GLOBAL DEVELOPMENTAL DELAY	4		63
98	0.01	1	17	20/07/2016	AGE WITH SEVERE DEHYDRATION		4		160
99	4	1	0	21/07/2016	B CELL ALL WITH HYDROCEPHALUS		4		172
100	6	2		20/07/2016	GBS		4		101
101	0.07	1	11.35	04/08/2016	T CELL IMMUNODEFECIENCY	IMMUNODEFECIENCY	3		161
102	0.02	1	2.35	04/08/2016	SEPSIS WITH MENINGITIS		4		167
103	12	1		04/08/2016	SEPSIS WITH MENINGITIS		4		100
104	0.02	1	12.15	30/07/2016	SEIZURE DISORDER		4		110
105	0.02	2	10	30/07/2016	SEIZURE DISORDER		4		120
106	0.11	1	18.3	22/07/2016	RTA PROXIMAL		4	44.3	160
107	8	1		08/08/2016	FANCONI'S ANEMIA	FANCONI'S ANEMIA	4		160
108	0.02	1	2	06/08/2016	RETROPHARYNGEAL ABSCESS		4		107
109	9	1		05/08/2016	PARTIAL HANGING	NIL	4	85.6	113
110	6	1	8	20/06/2016	RTA		4	18.3	118
111	14	2	22	15/06/2016	DISSEMINATED TUBERCULOSIS		3		106
112	6	1	9.3	19/06/2016	STATUS EPILEPTICUS		4		150
113	7	2		10/08/2016	ATYPICAL HUS		4		114
114	0.07	2	3	12/08/2016	ACUTE GASTROENTERITIS WITH SEVERE DEHYDRATION	NIL	4		179
115	0.01	2	12	09/08/2016	ACUTE GASTROENTRITIS WITH SEVERE DEHYDRATION		4		123
116	7	1	11.3	11/08/2016	AYPICAL HUS		4		117
117	4	1	19.3	09/08/2016	NEPHROTIC SYNDROME		4		158
118	7	1	10.3	10/08/2016	SEIZURE DISORDER, ASPIRATION PNEUMONIA		4		128
119	0.03	1		12/08/2016	PNEUMONIA	NIL	4		149
120	2	2	20.3	02/07/2016	KEROSENE POISONING		4		145
121	1	1		27/07/2016	STAPHYLOCOCCAL SEPSIS WITH SHOCK, ARDS		4		128
122	12	2		21/08/2016	IC BLEED, WARFARIN OVERDOSE, MITRAL VALVE REPLACEMENT	MITRAL VALVE REPLACEMENT	4		126
123	12	2		19/08/2016	DIPHTHERIA	NIL	4		
124	0.01	1		19/08/2016	AZRA'S BABY	NIL	4		
125	3	2	23.3	14/08/2016	ARDS	NIL	4		

125	20	22	100	100	60	40	7	8		181		1.7		3.2		250		452	2	1
109	20	31	100	100	60	60	11	11	227	160	2.9	4.1	6.6	6.6	166	166	378	266	2	2
151	20	17	100	100	60	60	16	10		190		3.1		6		166		316	2	1
167		45		94		90		12		126		8.5		11.4		104		144	2	3
115	29	30	100	97	75	75				80						129		106	2	1
	58		97		80				87						121		108		1	2
140	25	40	100	100	60	60	10	8		195		2.4		4.8		166		325	2	1
167	41	30	90	100	100	70	11	15		85		12.5		10.5		142		121	1	2
123	18	25	99	99	60	45	12	10		219		2		4.5		220		486	2	1
80	35	34	100	100	60		10		97		6.1			6	166		166		2	1
	26		100		70		7		310		1.5		4.9		142		442		2	3
135	28	17	97	100	40	55	10	9		188		2.6		4.9		181		341	2	2
	25		100		100		15		109		13.7		15		100		109		2	1
149	41	25	100	98	86	30	9	7		161		1.3		2.1		326		536	2	3
104	35	35	100	100	60	45	11	12		180		3		5.4		222		400	2	1
80	20	15	100	100	60	40	20	17		175		4.5		8		250		435	2	1
140	44	35	94	100	60	50	7	7	216	258	1.9	1.3	4.4	3.5	156	200	360	516	2	3
115	27	25	98	100	60	60	12	11	88	106	8.1	6.2	7.3	6.6	163	166	146	176	2	3
	25		100		60				303						166		505		2	1
107	25	27	100	100	100	60	8	9		161		3.3		5.4		166		268	2	1
102	20	20	100	100	50	40	9	8	120	141	3.8	2.2	4.5	3.2	200	250	240	352	2	1
126	27	25	96	95	80	80	7	8	102		5.4		5.8		120		127		2	1
125	16	16	100	100	100	40	9	8		154		2.1		3.2		250		385	2	2
147	27	23	100	96	60	40	7	10	116	100	3.6	4	4.2	4.1	166	240	193	250	2	1
106	31	27	99	100	50	35	11	7	245		2.2		5.5		198		490		2	1
148	32	33	100	100	60	50	6	12		296		2		6		200		592	2	2
157	19	15	100	100	100	70	19	13	191	128	9.9	7.1	19	91	100	142	191	163	2	3
	21		100		40		13		139		3.7		52		2.5		347		2	1
114	40	45	100	100	50	50	11	7	189	200	2.9	1.8	5.5	3.5	200	200	378	200	2	2
	20		98		50		8		166		2.4		4.1		196		332		2	1
121	23	30	100	100	60	40	6	9	149	162	2.4	2.2	3.6	3.6	166	250	248	405	2	2
117	33	22	100	100	80	80	11	10	145	100	6	8	8.8	8	125	125	181	125	2	3
153	34	45	100	100	60	50	9	10	133	140	4.1	3.5	5.4	5	166	200	221	280	2	2
	31		100		70		12		243		3.5		8.4		142		347		2	3
71	20	18	100	100	60	40	7	7		194		1.4		2.8		250		485	2	3
157	40	27	96	100	75	35	8	11		271		1.4		3.9		285		774	2	1
180	15	26	100	100	40	30	4	4		203		0.6		1.2		333		676	2	2
120	19	20	100	100	88	86	17	17	88	86	11.5	10.8	1	9.3	166	181	146	156	2	1
148	30	41	100	100	100	60	16	15	84	385	19	2.3	16	9	100	166	84	641	2	1
127	27	17	100	100	60	35	7	7		156		1.6		2.5		285		445	1	1
127	18	17	100	100	60	35	7	7	171	172	2.4	1.4	4.2	2.5	166	285	285	494	2	1
133	25	40	100	100	60	60	8	7	206	139	2.3	3.2	4.8	4.2	166	166	343	231	2	1
135	30	45	98	100	90	50	8	9	211	153	3.4	4.5	7.3	4.5	108	200	234	306	2	1
139	29	26	100	100	100	501	8	8	143	143	5.5	2.7	8	4	100	200	143	286	2	3
	37		88		100		19												2	2
	26		100		100		8		173		4.6		8		100		173		2	1
119	28	19	100	100	80	40	10	8	336	84	2.3	3.8	8	3.2	125	250	420	210	2	1
74	20	30	100	100	60	35	7	9	292	177	1.4	1.7	4.2	3.1	166	285	480	505	2	1
135	45	41	96	96	60	45	9	7	195	97	2.7	3.2	5.6	3.3	160	213	325	215	2	1
148	20	25	100	96	60	40	10	8	169	139	3.5	2.3	6	3.3	166	240	281	347	2	2
	38		85		100		68		470		14.4		68		85		470		1	2
	23		100		35		8		96		2.9		2.8		285		274		2	1
104	35	31	92	97	100	60	7	10	90	400	7.7	1.5	7.6	6.1	92	161	90	666	2	1
	29		100	100	9	50	9	7	82	404	10.9	0.9	9	3.5	100	200	82	808	2	1
	24		90		100		16		186		8.6		17.7		90		186		2	1
117	16	15	100	100	100	40	10	6	106	157	9.4	1.5	10	2.4	100	250	106	392	2	1
	25		100		60		7		89		4.7		4.2		166		89		2	1
	20		100		65		15		198		4.9		9.8		153		304		2	1
149	25	25	98	98	50	60	22	22	112	125	9.8	10.5	11.2	13.4	196	163	196	163	1	3
145			100	100	50	30	8	8	131		3		4		200		262		2	3
			100	100	60	60	15	16	139	162	6.4	5.9	9	9.6	166	166	231	270	2	2
			100	96	60	60	35	25	120	214	17.5	7	21	15.6	166	166	200	356	2	2
			100	981	100	60	10	13	217	168	4.6	4.6	10	8	100	163	217	280	1	3